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Evaluation of HHV6 reactivation in gastric biopsy and blood samples in patients underwent allogeneic stem cell transplant (HSCT) for hematological malignancies: results from a retrospective single center analysis

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Introduction/Summary

- Human herpesvirus 6 (HHV6) is a lymphotropic that belongs to the beta-herpesviruses and the seroprevalence in the adult population is universally >95%. Two major subgroups of HHV-6 variant A and variant B have been identified. Polymerase chain reaction is the test of choice for HHV-6 diagnosis after HSCT, HHV6-DNA detection in whole blood samples usually indicates virus replication but in a lower percentage of cases persistently high levels of HHV6 DNA could indicate a positive donor and/or recipient chromosomally-integrated-HHV6 status (ciHHV-6). Although HHV-6 is a lymphotropic virus, it uses CD46 as a receptor and may also infect other cell types, such as monocytes and endothelial and epithelial cells, HHV-6 can cause graft dysfunction. In stem cell transplant recipients with gastrointestinal symptoms, HHV-6 DNA has been detected by PCR in gastroduodenal and colorectal mucosa. Herpes virus 6 reactivation occurs in 30-80% of patients underwent HSCT usually within the first 6 weeks and was associated with delayed engraftment, grade III/IV acute graft versus host disease (aGVHD) and all-cause-mortality.

Study Design

- Since the virus persists in the host in a latent form after primary infection and reactivation occur in about 30-80% of patients underwent HSCT and was associated with several complications. In allogeneic stem cell transplant (allo-SCT) recipients with gastrointestinal symptoms, HHV-6 DNA has been detected by PCR in gastroduodenal and colorectal mucosa.

  The aim of this study was to investigate the significance of presence of HHV-6 DNA in patients who underwent endoscopic examination because of upper gastrointestinal symptoms after allo-SCT.

Results

- From 2022 to 2023 a total of 96 patients underwent HSTC. We found 46 cases of grade 1-4 aGVHD and 18 cases of grade 2-4 aGVHD. Moreover 9 patients developed Gastrointestinal (gi-GVHD) proved by histology. Median day of endoscopy was 50 (13-115). Patients characteristics are shown in Table 1.

Table 1 **Patients characteristics**

PATIENTS CHARACTERISTICS	
Median day Endoscopy from HSCT	50 (13-115)
Patient Age (yrs)	53 (19,9-73)
Engraftment day (ANC>500)	16 (13-21)
Recipient sex F	7/15 (46%)
DIAGNOSIS	N. of patients
Acute myeloid leukemia Acute lymphoblastic leukemia Myelodysplastic syndromes Lymphoma	8 (53%) 3 (20%) 3 (20%) 1(7%)
DISEASE STATUS	**N. of patients**
First Complete Remission Second Complete Remission Third Complete Remission Active disease	10 (67%) 1 (7%) 1 (7%) 3 (20%)
DONOR	**N. of patients**
Matched Related Donors Matched unrelated donor Haplo-identical related donor Mismatched unrelated donors	0 5 (33%) 8 (53%) 2 (13%)
CONDITIONING	**N. of patients**
Myeloablative conditioning Reduced-intensity conditioning	11 (73%) 4 (28%)

methotrexate, CSA: cyclosporine, PTCY: post transplant cyclophosphamide, MMF: mycophenolate mofetil

One patient with g-aGVHD was negative. In table 2 gastric HHV6 fundus, body or duodenum positivity plotted with g-aGVHD histology. Eleven patients were HHV6 positive but did not satisfy diagnostic criteria for g-aGVHD and, finally one patients was negative for HHV6 and did not had diagnostic criteria for g-aGVHD. In the whole cohort 100-day and 1-year Non-Relapse Mortality (NRM) were 7 and 29% respectively. 100 days and 1 year overall survival was 93% and 64 % respectively in the whole cohort. 9 months NRM was 8% vs 33% p=0,06463 in patients with fundus HHV6 copy number under and above median value respectively. There was no difference in survival comparing groups with HHV6 log value above and under median.

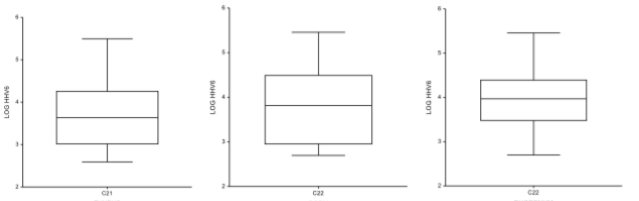

Figure 1. The logaritmic transformation of the quantitative detection of HHV6 copies/ml was 3,6 (2,59-5,49); 3,8 (2,69-5,45), 4,1 (2,89-5,3) in samples from fundus, body and duodenum respectively

Table 2 HHV6 DNA Detection

	HHV6 DNA +	HHV6 DNA +
aGVHD +	n. 2	n. 1
aGVHD -	n. 11	n. 1

Gastric HHV6 DNA detection in biopsy of fundus, body or duodenum plotted with g- aGVHD histology

Methods

- We retrospectively analyzed data from 16 patients grafted with allogeneic peripheral blood stem cell transplant from 2022 to 2023 who underwent gastroscopy because of persistent nausea/vomiting. The biopsy of fundus, body and duodenum were analysed by conventional histology for presence of GVHD and by quantitative polymerase chain reaction (PCR) for viral DNA of HHV 6 A and B (HHV6 ELITe MGB Kit, Elitech). The molecular test was performed both on gastric biopsy and peripheral blood. All statistical analysis was performed with NCSS 2019 software.

The analysis of HHV6 DNA detection showed 12 patients having positivity in fundus, 11 in body, 8 in duodenum and 1 peripheral whole blood. After logarithmic transformation, HHV6 copies was 3,6 (2,59-5,49); 3,8 (2,69-5,45), 4,1 (2,89-5,3) in samples from fundus, body and duodenum respectively (Fig1). No correlation was found between acute GVHD (aGVHD) grade and log HHV6 fundus positivity. Only 2 patients with fundus HHV6 positivity had a proven histologic diagnosis of gastric aGVHD(g-aGVHD).

Conclusion

- We did not find correlations between aGVHD grade and LOG HHV6 fundus positivity not between gastric acute GVHD histology and HHV6 positivity. We found a positive trend between HHV6 copy number in samples from fundus and NRM. Further prospective analysis could elucidate role of gastric HHV6 reactivation on HSCT outcome

References

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