IMMUNE COMPLICATIONS OF ALLOGENEIC HEMATOPOIETIC STEM CELL TRANSPLANTATION: PRE-TRANSPLANT COVID-19 INFECTION INCREASES THE RISK OF HEMOPHAGOCYTIC LYMPHOHISTIOCYTOSIS

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is an acute, rapidly progressive and life-threating systemic inflammatory process.

1) **primary (or familiar) HLH - inborn (specific genetic mutations)**
2) **secondary (or reactive) HLH - acquired (immunocompromised hosts with dysfunction of adaptive immunity) - use of HScore to estimate diagnosis[1]**

Malignancies and autoimmune disorders (and their treatment) represent the major causes of reactive HLH[2,3]. However, infections (including COVID-19) are considered to trigger this process[4]. Patients after allogeneic hematopoietic stem cell transplantation (alloHSCT) belong to the group of patients with the most vulnerable and dysfunctional adoptive immunity. Comparing to previous two decades, there was observed a relatively high incidence of reactive HLH in patients who had undergone allografting in the COVID-19 pandemic years 2020 and 2021.

Aim of Study

To assess an association between COVID-19 infection and reactive HLH in the patients treated with alloHSCT.

Null hypothesis: ***„Previous COVID-19 infection does not increase the risk of post-transplant reactive HLH development.“***

Patients and Methods

37 patients with an age median of 45 (range, 18-64) years underwent alloHSCT for various hematologic diseases in the years 2020 and 2021. The median of post-transplant follow-up was 314 (38-790) days. A diagnosis of reactive HLH was established using the HScore. The impacts of pre-, peri- and post-transplant factors including COVID-19 infection on the HLH development were evaluated by the methods of univariate (Fisher´s Exact Test, Mann-Whitney U-Test, Kaplan-Meier´s Method) as well as multivariate (Cox Proportional-Hazards Regression) statistical analysis.

Results

Pre- and post-transplant COVID-19 infections were confirmed in 7 (18.9%) and 8 (21.6%) recipients, respectively. HLH was observed in 12 (32.4%) patients at the median of 70 (14-220) days after alloHSCT. The medians of the HScore and probability of reactive HLH were 236 (205-282) and 98% (88-99%), respectively. Previous COVID-19 infection, lower post-transplant absolute lymphocytes counts (ALC) and IgG levels were the only predictors significantly associated with HLH development after alloHSCT in univariate analysis (***Table 1***). Multivariate analysis confirmed lymphocytopenia (ALC < 0.8 x10^9/L) and pre-transplant COVID-19 infection as the only independent predictors of post-transplant reactive HLH risk (***Table 2***).

Table 1. ***Predictors of post-transplant reactive HLH (univariate analysis)***

significant parameter	patients with HLH (12)	patients without HLH (25)	p-value
pre-transplant COVID-19 infection	5 (41.7%)	2 (8%)	*0.03*
post-transplant ALC (median)	0.5 (0.05-1.1) x10^9/L	1.2 (0.05-2.8) x10^9/L	*0.002*
post-transplant IgG (median)	5.4 (3.6-12.9) g/L	8.7 (0-14.2) g/L	*0.007*

Table 2. ***Predictors of post-transplant reactive HLH (multivariate analysis)***

covariates - evaluated parameters	Risk Ratio (RR)	95% Confidence Interval	p-value
pre-transplant COVID-19 infection	5.32	1.47-19.25	*0.01*
post-transplant ALC < 0.8 x10^9/L	8.33	1.37-50	*0.02*
post-transplant IgG < 6.1 g/L	1.44	0.37-5.56	0.6

Significantly higher risk of HLH development in the recipients with COVID-19 infection history was demonstrated by probability HLH-free survival (defined as time interval from alloHSCT to HLH manifestation, censored to the date of the last follow-up) as well (***Figure 1***). Interestingly, there were also observed some cases with neurological symptoms due to brain white matter involvement (***Figure 2***) as well as complete resolution of leukemic cell population in the patient with post-transplant persistence of acute myeloid leukemia (AML) early after onset of HLH (***Figure 3***).

Figure 1. ***HLH-free survival***

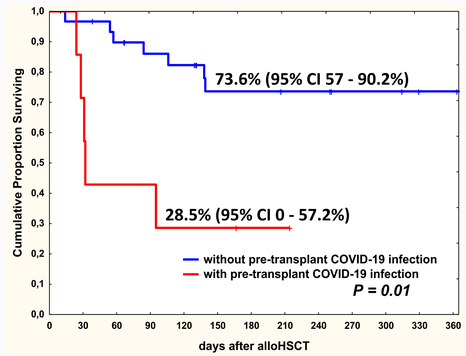

Figure 2. ***Brain white matter involvement in reactive HLH***

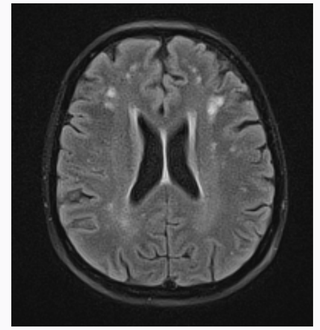

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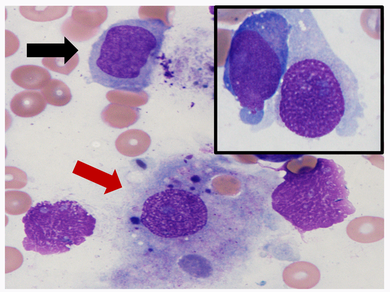
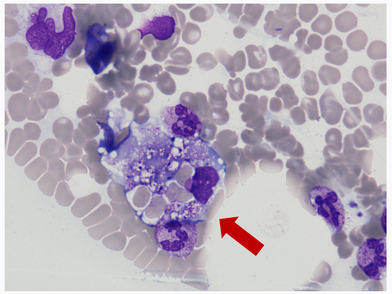
Figure 3. ***Hemophagocytosis and blasts clearance in the bone marrow of a patient allografted for recurrent AML***



A. Persisting leukemic myeloblasts (black arrow), hemophagocytosis (red arrow) and incipient phagocytosis of blast (window) on day +21



B. Hemophagocytosis (red arrow) without an evidence of leukemic myeloblasts in bone marrow smear on day +35 (patient achieved remission of AML)

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Conclusion

Presented results did not confirm formulated null hypothesis. Allografted patients with history of COVID-19 infection and severely impaired adaptive immunity might be in significant risk of post-transplant reactive HLH.

SVOČ Conference 25th May of 2022

References

1. Fardet L, Galicier L, Lambotte O, et al. Development and Validation of the Hscore for the Diagnosis of Reactive Hemophagocytic Syndrome. Arthritis Rheumatol 2014, 66, 2613-2620.
2. Daver N, McClain K, Allen CE, et al. A consensus review on malignancy-associated hemophagocytic lymphohistiocytosis in adults. Cancer 2017, 123, 3229-3240.
3. Fattizzo B, Ferraresi M, Giannotta JA, Barcellini W. Secondary Hemophagocytic Lymphohistiocytosis and Autoimmune Cytopenias: Case Description and Review of the Literature. J Clin Med 2021, 10, 870.
4. Kanematsu E, Nunokawa T, Chinen N, Komatsu A. Late-onset COVID-19-induced Hemophagocytic Syndrome. *Intern Med* 2021, 60, 3511.

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