News Release

Title

Publication of frequent genetic abnormalities of immune checkpoint-related genes in intravascular large B-cell lymphoma ~Detection of genetic alterations using cell-free DNA in a rare type of malignant lymphoma~

Key Points

• Cell-free DNA (cfDNA) exists in higher concentrations in patients' plasma with intravascular large B-cell lymphoma (IVLBCL), and cfDNA can be used as an alternative source of comprehensive genetic analyses leading to uncovering the characteristics of genetic abnormalities in IVLBCL.

• The characteristic of genetic abnormalities in IVLBCL was similar to "MCD type", which is one of genetic subtype in diffuse large B-cell lymphoma (DLBCL), and frequent genetic alterations of immune evasion related genes such as *PD-L1* and *PD-L2* were identified.

• The result of this research demonstrates the usefulness of "liquid biopsy" in IVLBCL. The result also provides important findings for the development of future targeted therapies.

Summary

Professor Akihiro Tomita (Professor, Department of Hematology, Fujita Health University School of Medicine), Kazuyuki Shimada (Lecturer, Department of Hematology, Nagoya University Hospital), Professor Hitoshi Kiyoi (Professor, Department of Hematology and Oncology, Nagoya University Graduate School of Medicine), Professor Seishi Ogawa (Professor, Department of Pathology and Tumor Biology, Graduate School of Medicine, Kyoto University), and Kenichi Yoshida (Assistant Professor, Department of Pathology and Tumor Biology, Graduate School of Medicine, Kyoto University) focused on the cell-free DNA from lymphoma cells in IVLBCL patients' plasma, and then clarified the characteristics of genetic abnormalities in IVLBCL.

Malignant lymphoma is one of hematological malignancy known to be quite heterogenous. IVLBCL is a rare type of malignant lymphoma characterized by the lack of lymphadenopathy; which makes accurate diagnosis difficult. In general, the diagnosis of malignant lymphoma is performed by tumor mass biopsy. However, IVLBCL normally lacks tumor mass, therefore skin, bone marrow (BM) and other organs are randomly biopsied for diagnosis of IVLBCL when a disease is suspected. The diagnosis of IVLBCL was made by finding a small number of lymphoma cells in the lumina of small vessels in tissues obtained at biopsies. In addition, the difficulty to obtain sufficient lymphoma cells from the biopsy specimens has hampered a research to uncover the underlying biology of IVLBCL.

In this study, we investigated cfDNA in patients' plasma with IVLBCL, and discovered the existence of cfDNA in higher concentrations. Moreover, cfDNA in IVLBCL patients allowed us to perform the comprehensive genetic analysis. The analyses clarified genetic characteristics of IVLBCL, and also revealed frequent alterations of immune evasion related genes such as *PD-L1* and *PD-L2*. The result of this research demonstrates the usefulness of liquid biopsy in IVLBCL to detect the disease, and the possibility of cfDNA as a source in monitoring the disease status. This research was published in the Blood on December

24, 2020 at 13:00 GMT.

Research Background

IVLBCL is a rare type of malignant lymphoma characterized by the lack of lymphadenopathy. The disease develops with non-specific clinical symptoms such as persistent fever and general fatigue, whose diagnosis is often difficult even for well-trained hematologists. The delay of precise diagnosis makes disease progress leading to the poor prognosis in patients with IVLBCL. Therefore, a breakthrough to promptly detect the disease had been desired. Moreover, to clarify the genetic characteristics of the disease for the development of the future targeted therapies in IVLBCL had been also desired.

Research Results

To uncover the genetic characteristic of IVLBCL, we performed whole-exome sequencing (WES) of 21 patients with IVLBCL using plasma-derived cfDNA (n = 18), patient-derived xenograft tumors (n = 4), and tumor DNA from BM mononuclear cells (n = 3). The concentration of cfDNA in IVLBCL was significantly higher than that in DLBCL ($P < 0.0001$) and healthy donors ($P = 0.0053$), allowing us to perform WES, and most mutations detected in BM tumor DNA were successfully captured in cfDNA and xenograft. IVLBCL showed a high frequency of genetic alterations similar to activated-B-cell-type DLBCL; with the former showing conspicuously higher frequencies of mutations in *MYD88* (57%), *CD79B* (67%), *SETD1B* (57%), and *HLA-B* (57%). We also found that 38% of IVLBCL harbored rearrangements of *PD-L1*/*PD-L2* involving the 3′-UTR; such rearrangements are implicated in immune evasion via *PD-L1*/*PD-L2* overexpression.

Research Summary and Future Perspective

This study provides the usefulness of cfDNA for IVLBCL patients. Considering the difficulty of diagnosis in IVLBCL, cfDNA can be a promising source to support timely diagnosis of IVLBCL. Moreover, to clarify genetic characteristics of IVLBCL can lead to the development of novel therapeutics based on the genetic abnormalities. Especially, the frequent alterations of immune evasion related genes might result in the development of novel treatment strategy using immune-checkpoint inhibitors.

Publication

Blood

Frequent Genetic Alterations in Immune Checkpoint-Related Genes in Intravascular Large B-Cell Lymphoma

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