HGG-50. TWO CASES OF H3 K27M-MUTANT DIFFUSE MIDLINE GLIOMA OF CERVICAL SPINAL CORD

Masae Kuroha[1], Kaoru Tamura[1], Motoki Inaji[1], Satoka Hashimoto[1], Daisuke Kobayashi[2], Yoji Tanaka[1], Tadashi Nariai[1], and Taketoshi Maehara[1]; [1]Department of Neurosurgery, Tokyo Medical and Dental University, Tokyo, Japan, [2]Department of Pathology, Tokyo Medical and Dental University, Tokyo, Japan

BACKGROUND: "Diffuse midline glioma, H3 K27M-mutant' was newly categorized as a separate pathological entity in the 2016 WHO classification, based on recently discovered mutation. Spinal cord glioma with H3 K27M-mutant is rare, so we reported the clinical course of two cases. CASE 1: A 17-year-old male presented with posterior headache and right limbs paralysis. MRI showed cervical spinal cord with expansion, T2-weighted high intensity and a part of enhancement. The biopsy revealed a diffuse midline glioma, H3 K27M-mutant. He received bevacizumab plus radiotherapy-temozolomide. In a few months, he had quadriplegia and cranial nerve paralysis and needed respirator. There was not expansion of mass, but intracranial dissemination. CASE 2: A 16-year-old male presented with posterior neck pain and right limbs paralysis. On brain stem and cervical spine, MRI findings were same to case 1. The biopsy was undergone and revealed H3 K27M mutation. He received bevacizumab in addition to radiotherapy-temozolomide. Although he also had quadriplegia, the progression of tumor has stopped. He has received chemotherapy with respirator at home. DISCUSSION: It was previously reported that the prognostic factors for diffuse midline glioma were tumor location, H3 K27M-mutation and age, but there are few relevant studies. The consensus on the treatment is also not clearly determined. Because the cervical spinal cord gliomas are rapidly advanced miserably, we added bevacizumab to standard radiotherapy-temozolomide for initial treatment. In addition, whole brain and spine radiation may be considered to avoid dissemination. Multicenter study is important to collect information and improve treatment of H3 K27M-mutant glioma.

HGG-51. PAIRED EPITHELIOID GLIOBLASTOMA PATIENT DERIVED XENOGRAFT MODELS WITH/WITHOUT MOLECULAR TARGET THERAPY

Jo Sasame, Kensuke Tateishi, Naoki Ikegaya, Yohei Miyake, Shigeta Miyake, Taishi Nakamura, and Tetsuya Yamamoto; Department of Neurosurgery Yokohama City University, Yokohama, Kanagawa, Japan

Epithelioid glioblastoma (E-GBM) predominantly arises at younger age and promotes dismal prognosis. Because of its rare etiology, pathological and genetical characterization of E-GBM remains elusive. Herein, we report 2 patient-derived E-GBM xenograft (PDX) models from young adult patients (YMG62 and YMG89) with *BRAFV600E* and *TERT* promoter mutation. The YMG62 patient received dabrafenib with trametinib, while YMG89 patient received dabrafenib monotherapy after recurrence with Stupp regimen. These molecular target therapies were initially responded, but gradually became resistant (YMG62R and YMG89R) and resulted in lethal. Treatment resistant cells were collected from CSF. These primary cells were propagated at multiple passage *in vitro*. Paired PDX models were established from initial and recurrent cells. All PDX tumors were preferentially disseminated and negative expression of GFAP, which were recapitulated to the patient characteristics. BRAF and MEK inhibitor moderately suppressed cell viability of YMG62 and YMG89 *in vitro*. However, BRAF and MEK inhibitor became resistant at recurrence *in vitro*. Western blotting indicated retained phospho-MEK expression after BRAF/MEK inhibitor treatment in recurrent cells, which implies crucial role of MEK activation for tumor maintenance in *BRAFV600E* mutant E-GBM. Together, paired E-GBM PDX models with/without molecular target therapy recapitulate patient characteristics, which may contribute to elucidate tumor biology and establish novel therapeutic target in E-GBM.

HGG-52. SUSTAINED RESPONSE TO CRIZOTINIB MONOTHERAPY IN AN INFANT WITH GOPC-ROS1 FUSED CONGENITAL HEMISPHERIC GLIOMA

Rishi Lulla[1], Konstantina Svokos[2], Kristine Pelton[3], Douglas Anthony[4], Mehdi Touat[3], and Keith L. Ligon[3]; [1]Department of Pediatrics, The Warren Alpert School of Medicine at Brown University, Providence, RI, USA, [2]Department of Neurosurgery, The Warren Alpert School of Medicine at Brown University, Providence, RI, USA, [3]Department of Oncologic Pathology, Dana-Farber Cancer Institute, Boston, MA, USA, [4]Department of Pathology, The Warren Alpert School of Medicine at Brown University, Providence, RI, USA

Recent studies identified the presence of *ALK/ROS/NTRK/MET* alterations in a subset of infantile hemispheric gliomas. We report a case of GOPC-ROS1 fused congenital hemispheric glioma with a sustained response to crizotinib. An infant born at 28 weeks gestation was diagnosed with a large hemispheric mass at 2 weeks of life. The tumor was partially resected at 7 weeks of life. Histological evaluation confirmed a neoplasm with a spindle cell growth pattern, hypercellularity, nuclear pleomorphism, endothelial proliferation and necrosis consistent with glioblastoma. Fresh tissue was submitted for targeted panel sequencing (Oncopanel) which identified the presence of a GOPC-ROS1 fusion (exon 36:intron 4). This was confirmed by copy number analysis which showed a focal intragenic deletion with a breakpoint in ROS1 on 6q22. Given the lack of preclinical native models for ROS1 and other congenital kinase-driven gliomas, live cells were utilized to attempt to establish a patient derived cell line (organoid/neurosphere model) and intracranial patient derived xenograft model, the results of which are pending and will be reported. The GOPC-ROS1 rearrangement was structurally predicted to respond to kinase inhibitors with activity against ROS1 and crizotinib was started at 280 mg/m2/dose twice daily at 6 months of life with progressive tumor noted on imaging. Three months after initiating therapy, a 56% reduction in the tumor size and subsequent imaging revealed additional response. Our report is the first to demonstrate clinical response to crizotinib in a GPOC-ROS1 fused congenital glioblastoma and describe the development of a renewable resources for future analysis.

HGG-53. PROJECT HOPE: "PEDIATRIC AND AYA HIGH-GRADE GLIOMA OMICS PROJECT"- A LONGITUDINAL MOLECULAR LANDSCAPE OF HIGH-GRADE GLIOMAS RESOLVED AT SINGLE-CELL LEVEL

Olivia A. Hack[1,2], Husam Babikir[3], Li Jiang[1,2], Karin Shamardani[3], Ilon Liu[1,2], McKenzie Shaw[1,2], Kennedy Cunliffe-Koehler[4], Adam Resnick[5], Michael Prados[3], Michelle Monje[4,6], Aaron Diaz[3], and Mariella G. Filbin[1,2]; [1]Department of Pediatric Oncology, Dana-Farber Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA, [2]Broad Institute of Harvard and MIT, Cambridge, MA, USA, [3]Department of Neurological Surgery, University of California, San Francisco, San Francisco, CA, USA, [4]Department of Neurology, Stanford University, Stanford, CA, USA, [5]Center for Data Driven Discovery in Biomedicine, Children's Hospital of Philadelphia, Philadelphia, PA, USA, [6]Department of Neurosurgery, Stanford University, Stanford, CA, USA

High-grade gliomas (HGG) are among the most prevalent and fatal cancers in pediatric, adolescent, and young adult (AYA) patients. Especially understudied are older children and young adults, aged 16–39 years. Previously, we profiled primary pediatric HGGs through single-cell transcriptomics and identified the genetic, epigenetic and developmental programs that drive their malignant progression. However, the questions of how these programs compare to those in older HGG patients, what the mechanisms are by which these tumors ultimately evolve to drive recurrence and treatment resistance, and how distinct tumor cell subpopulations bidirectionally communicate with their microenvironment remain to be elucidated. Here, we use single-nucleus RNA sequencing to compare 11 paired, matched high-grade gliomas at diagnosis and recurrence and 15 additional H3K27M primary and recurrent DMG samples in pediatric and AYA patients. In all tumors, we find both undifferentiated and differentiated tumor cells recapitulating distinct glial lineages, as well as diverse microenvironmental cell populations. When longitudinally comparing this tumor architecture within matched pairs, we find substantial differences in transcriptional program expressions. Diagnostic samples include more differentiated, astrocyte-like tumor cells, while cells from recurrent samples more highly express ribosomal and heat-shock protein genes, suggesting tumor progression- and treatment-related shifts. Ongoing sequencing and analysis will allow for unprecedented insight into the evolutionary dynamics of pediatric and AYA high-grade gliomas as well as delineate differences in the biology of DMGs occurring in different age groups. This multi-institutional project was funded by the National Institute of Health.

HGG-54. HISTOLOGICAL AND MOLECULAR CHARACTERIZATION OF HIGH-GRADE BRAIN TUMORS SECONDARY TO TOTAL BODY IRRADIATION FOR HEMATOLOGICAL MALIGNANCIES

Evelina Miele, Daria Pagliara, Lucia Pedace, Francesca Diomedi Camassei, Antonella Cacchione, Giovanna Stefania Colafati, Andrea Carai, Franco Locatelli, and Angela Mastronuzzi; Bambino Gesù Children's Hospital, Rome, Italy

INTRODUCTION: Hematopoietic stem cell transplantation (HSCT) is increasingly used in the treatment of acute leukemias (AL), non-Hodgkin lymphomas and other primary malignancies. However, a growing number of neoplasms secondary to HSCT are reported. The combination of total body irradiation (TBI) and high dose chemotherapy (HD-CT) as conditioning regimen is considered a risk factor. We present four children who survived AL, treated with HSCT and conditioning regimens including TBI/HD-CT. These patients developed a high-grade-brain tumor. We analyzed histological and molecular characteristics of neoplasms. METHODS: Histologically, tumors were assessed for: presence of mitosis, necrosis and vascular proliferation; expression of ki67; expression of neuronal and glial markers, p53 and therapeutic targets. We analyzed the DNA methylation profile (DMP)