Diffuse midline glioma H3 K27-altered

- Histopathological grades as prognostic factors of H3 K27-altered diffuse midline glioma and their prediction using multiparametric MR imaging
- Incidental Diffuse Midline Glioma, H3 K27-Altered of the Pons Without Significant Coalterations
- Adult H3 K27-altered, H3.3 K27-mutant diffuse midline glioma affecting the conus medullaris: illustrative case
- Ara-C suppresses H3 K27-altered spinal cord diffuse midline glioma growth and enhances immune checkpoint blockade sensitivity
- Case Report: Rare intraventricular H3 K27-altered diffuse midline glioma in an adult
- Imaging the artery of Percheron: a pictorial review of associated pathology with important mimics of bithalamic abnormalities
- Characterizing the molecular and spatial heterogeneity of midline gliomas in adults: a single institution analysis
- Vanishing Contrast Enhancement of a Diffuse Midline Glioma

This subtype is characterized by mutations in the genes encoding histone H3 proteins, particularly the H3F3A or HIST1H3B genes, leading to a lysine-to-methionine substitution at position 27 (K27M). These mutations affect epigenetic regulation and are associated with poor prognosis. They are often found in midline gliomas arising in the thalamus, brainstem, or spinal cord.

Diffuse midline glioma (DMG), H3 K27M-mutant, was defined in the World Health Organization Classification of Tumors of the Central Nervous System 2016 grouping together diffuse intrinsic pontine gliomas and infiltrating glial neoplasms of the midline harboring the same canonical mutation at the Lysine 27 of the histone H3 tail.

In the past, pediatric diffuse gliomas were grouped with their adult counterparts, despite known differences in behavior between pediatric and adult gliomas with similar histological appearances. Information on the distinct underlying genetic abnormalities in pediatric diffuse gliomas is beginning to allow the separation of some entities from histologically similar adult counterparts.

One narrowly defined group of tumors primarily occurring in children (but sometimes in adults too) is characterized by K27M mutations in the histone H3 gene H3F3A, or less commonly in the related HIST1H3B gene, a diffuse growth pattern, and a midline location (e.g., thalamus, brain stem, and spinal cord). This newly defined entity is termed diffuse midline glioma, H3 K27M–mutant and includes tumors previously referred to as diffuse intrinsic pontine glioma (DIPG). The identification of this phenotypically and molecularly defined set of tumors provides a rationale for therapies directed against the effects of these mutations.

Epidemiology

Diffuse H3 K27M-mutant gliomas occur primarily in children but can also be encountered in adults.

Diagnosis

see Diffuse midline glioma H3 K27M-mutant diagnosis.

Differential diagnosis

Compared with gliomas in the midline without H3 K27-altered, The MRI findings and ADC value of Diffuse midline gliomas, H3K27-altered have some characteristics, which can help improve the diagnosis and differential diagnosis [1)].

After the start of the era of biopsy, Diffuse intrinsic pontine gliomas (DIPG)s bearing Histone H3K27 mutations have been reclassified into a novel entity, diffuse midline glioma, based on the presence of this molecular alteration. However, it is not well established how clinically diagnosed DIPG overlap with H3 K27-mutated diffuse midline gliomas, and whether rare long-term survivors also belong to this group [2)].

Treatment

see Diffuse midline glioma H3 K27-altered treatment.

Outcome

Diffuse Midline Glioma H3 K27-altered Outcome

Research

Contemporary survival endpoints: an International Diffuse Intrinsic Pontine Glioma Registry study [3)].

Eight patient-derived orthotopic xenograft models were obtained after direct stereotactic injection of a mixed cell suspension containing tumor cells and stromal cells in the brainstem or thalamus of nude mice and serially passaged thereafter. In parallel, we developed 6 cell-derived xenograft models after orthotopic injection of tumor-initiating cells cultured from stereotactic biopsies. Cells were modified to express luciferase to enable longitudinal tumor growth monitoring, and fluorescent reporter proteins to trace the tumor cells in the brain.These models do not form a tumor mass, they are invasive, show the H3K27 trimethylation loss in vivo and the tumor type diversity observed in patients in terms of histone H3 mutations and lineage markers. Histological and MRI features at 11.7 Tesla show similarities with treatment naïve human DIPG, and in this respect, both direct and indirect orthotopic

xenograft looked alike. These DIPG models will therefore constitute valuable tools for evaluating new therapeutic approaches in this devastating disease [4].

Trials

Intratumoral microdialysis sampling is an effective tool to determine brain entry of varied agents and could help to provide a better understanding of the relationship of drug permeability to DMG treatment responsivity. This is a non-randomized, single-center, phase 1 clinical trial. Up to seven young adult (18-39 years) patients with recurrent high-grade or diffuse midline glioma will be enrolled with the goal of 5 patients completing the trial over an anticipated 24 months. All patients will take abemaciclib pre-operatively for 4.5 days at twice daily dosing. Patients will undergo resection or biopsy, placement of a microdialysis catheter, and 48 hours of dialysate sampling coupled with timed plasma collections. If intratumoral tumor or brain dialysate sampling concentrations are >10nmol/L, or tumor tissue studies demonstrate CDK inhibition, then restart of abemaciclib therapy along with temozolomide will be administered for maintenance therapy and discontinued with evidence of radiologic or clinical disease progression. The poor survival associated with diffuse midline gliomas underscore the need for improved means to evaluate efficacy of drug delivery to tumor and peritumoral tissue. The findings of this novel study, will provide real-time measurements of BBB function which have the potential to influence future prognostic and diagnostic decisions in such a lethal disease with limited treatment options. Trial registration: Clinicaltrials.gov, NCT05413304. Registered June 10, 2022, Abemaciclib Neuropharmacokinetics of Diffuse Midline Glioma Using Intratumoral Microdialysis [5].

Case series

Diffuse Midline Glioma H3 K27-altered case series.

Case reports

An uncommon, infratentorial localization of adult H3 K27M-altered diffuse midline glioma arising in a particularly rare site (medulla oblongata). In addition to this unusual presentation, the lesion exhibited a substantial contrast enhancement and size decrease after dexamethasone, generating diagnostic dilemmas [6]

A 36-year-old man presented with subacute progressive cognitive and visual deterioration, and hydrocephalus requiring ventricular shunting. MRI revealed a diffusely infiltrating lesion with a gliomatosis cerebri growth pattern, multiple foci of contrast enhancement, and diffuse leptomeningeal involvement. Suboccipital craniotomy with exploration of the posterior fossa revealed a subtle capsular lesion infiltrating into the choroid plexus. Although histologically low-grade, the tumor was found to have an H3K27M mutation establishing the diagnosis.

In spite of diverse clinicopathologic characteristics, H3K27M-mutant diffuse midline gliomas are incurable, WHO grade IV lesions with poor prognosis. Yekula et al. discussed the case in the context of

a review of published reports of H3K27-mutant diffuse midline gliomas in adults. Findings late in the disease course may mimic inflammatory or infectious pathologies radiographically, and low-grade infiltrative neoplasms histologically.

The diverse clinical, radiographic and molecular features of H3K27M-mutant diffuse midline gliomas in adults remain to be completely characterized. A high index of suspicion is required to avoid missing the diagnosis. Early biopsy and detailed molecular characterization are critical for accurate diagnosis and patient counseling [7)].

References

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