Secondary H3K27 Altered Diffuse Midline Glioma in a Treated Case of Acute Lymphoblastic Leukemia: A Case Report

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Summary

H3K27 altered diffuse midline glioma is a distinct grade IV glioma as per the recent 2021 WHO classification of primary CNS tumors. Herein, we report a rare case of a 26-year-old male diagnosed with this after treatment of B cell Acute Lymphoblastic Leukemia (B-ALL) with a latency period of 5 years post cranial radiation therapy (PCI). A 26-year-old male presented to the Medical Oncology Department with complaints of tingling sensation in bilateral upper limb for 15 days. MRI brain with MR Spectroscopy and whole spine screening revealed multiple thick walled cavitary lesions in right posterior capsuloganglionic - thalamus and centrum semiovale region. He had a past history of treatment of Philadelphia negative B-ALL in 2018 at the age of 21 years with MCP 841 protocol. Near total resection (NTR) of brain lesion was done and histopathology revealed this diagnosis. He is planned for adjuvant radiation with temozolomide.

Keywords: H3k27 altered diffuse midline glioma, secondary cranial neoplasm, prophylactic cranial irradiation, acute lymphoblastic leukemia, chemotherapy

Introduction

H3K27 altered diffuse midline glioma is a distinct grade IV glioma as per 2021 World Health Organization (WHO) classification of primary Central Nervous System (CNS) tumors. It is considered as high grade tumor with highly aggressive nature regardless of histological features.[1] A number of risk factors have been described for CNS tumors like exposure to ionizing radiation, a stochastic effect of radiation and certain chemotherapeutic agents.[2] Herein we report a rare case of a 26 year old male diagnosed with H3K27 altered diffuse midline glioma after treatment of B cell Acute Lymphoblastic Leukemia (B-ALL) with a latency period of 5 years post cranial irradiation (PCI).

Case Report

A 26-year-old male presented to the department of Medical Oncology with complaints of tingling sensation in bilateral upper limb for 15 days which was insidious in onset and gradually progressive in nature. Clinical examination was unremarkable for any focal neurological deficit and higher mental functions were normal. He had past history of Philadelphia negative B-ALL in 2018 at the age of 21 years. He was treated with MCP 841 protocol consisting of multiagent chemotherapeutic agents like anthracyclines, antimetabolites, alkylating agents and steroid divided in phases like induction phase 1 and 2 which included PCI, reinduction, consolidation and maintenance. PCI was delivered with conventional 2D technique with a dose of 1800 cGy/10 fractions which was completed in 2018. Maintenance phase comprising 18 months of chemotherapy was completed in 2021 and was kept under observation thereafter.

Magnetic Resonance Imaging (MRI) Brain with MR Spectroscopy (MRS) and whole spine screening was done revealing multiple thick walled cavitary lesions in right posterior capsuloganglionic - thalamus and centrum semiovale region measuring 3.6x3.8x3.7 cm with 2 adjacent small nodular hyperintense lesions in right parietal white matter measuring 1.4x2.4 cm and part of subependymal periventricular region aspect of trigone of right lateral ventricle measuring 1.2x1.4 cm which were hyperintense on T2W, hypointense on T1W and FLAIR (Fluid Attenuated Inversion Recovery) images and MRS showing raised choline peak and reduced N Acetyl Aspartate (NAA) suggestive of glioma (Figure 1). After ruling out leukemic relapse by doing CSF microscopic and biochemical examination, cytology, flow cytometry which were unremarkable, investigations to rule out infective etiology by CSF culture for bacterial, fungal infection and Cartridge-based nucleic acid amplification

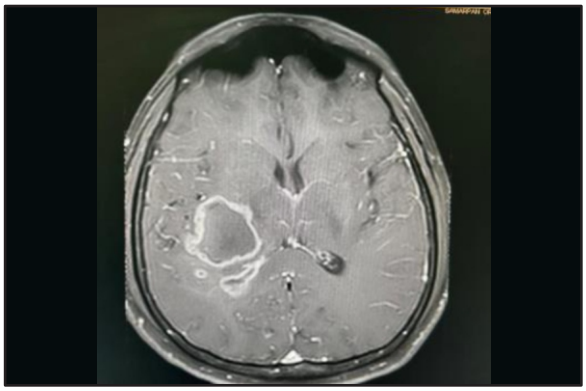

Figure 1: T1W MRI image with contrast enhancing hyperintense lesion

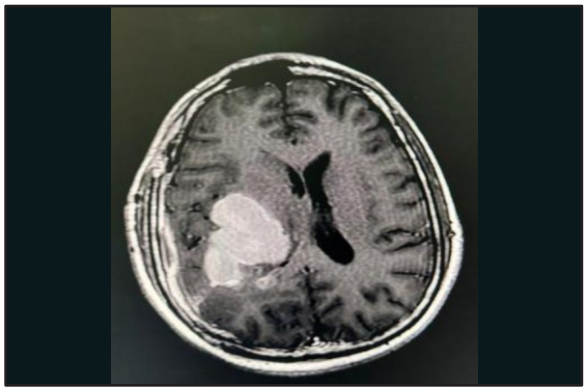

Figure 2: Postoperative T1W MRI with postoperative edema and hemorrhage with nodular residual lesion

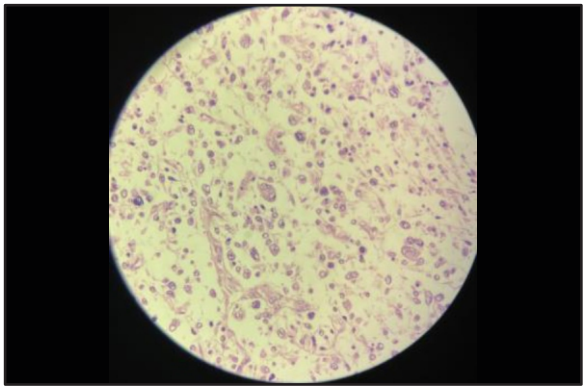

Figure 3: Morphological features of glioma

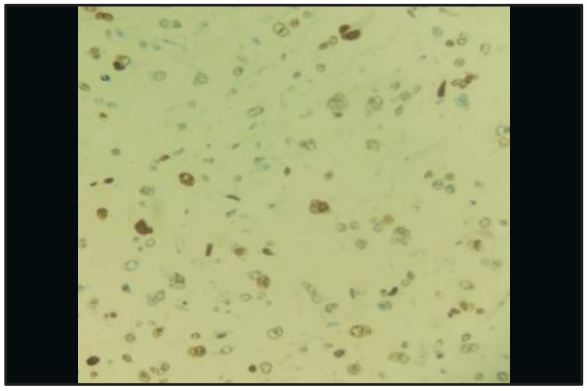

Figure 4: IHC featuring H2K27M alteration

testing (CBNAAT) for tuberculosis were done which were negative. To ensure remission from leukemia, bone marrow aspiration and trephine bone biopsy were done showing marrow in remission and scrotal ultrasound which revealed bilateral normal testis. Neurosurgical consultation was advised for procuring tissue for diagnosis; however patient consulted neurosurgeon elsewhere outside our institute where he underwent near total resection (NTR) of brain lesion through right parieto-temporal craniotomy approach in piecemeal fashion which was sent for histopathological examination. Postoperative clinical examination revealed no neurological deficit. Post-operative MRI brain revealed 2 small nodular residual lesions of 8x10 mm and 6x7 mm with surrounding oedema (Figure 2).

The slides and blocks were reviewed by the oncopathology department of our hospital and the histopathological features were suggestive of diffusely infiltrating tumor cells with marked pleomorphism, increased mitotic activity and endothelial cell proliferation (Figure 3). Immunohistochemical (IHC) markers showed positivity for markers: GFAP, altered H3K27, ki 67 of 10% and negative for CD20, CD3, LCA, CD34, MPO, Tdt and IDH1 R132H (Figure 4) which confirmed the final diagnosis of H3K27 altered Diffuse Midline Glioma, WHO grade 4. Postoperative hematoma was managed conservatively. Patient was thereby referred to the medical oncology department for further care. Patient is planned for adjuvant radiation by Intensity Modulated Radiotherapy (IMRT) at a dose of 180 cGy per fraction to a total dose of 5940 cGy concurrent with temozolomide.

Discussion

Several causative factors are responsible for secondary CNS tumors in ALL patients, including PCI, intrathecal and intravenous chemotherapy, genetic predisposition, and young age at diagnosis. Neoplasms of glial origin predominate, including anaplastic astrocytoma and glioblastoma. Cahan's criteria[3] aid in the diagnosis of radiation induced secondary neoplasms, modified by Schrantz and Araoz[4] as following (1) the tumor must appear within the previously irradiated field, (2) Not present prior to the radiotherapy, (3) a sufficient latency period must have been elapsed between irradiation and appearance of the tumor (usually > 5 years), and (4) must be histologically proven and of different histological type from the original neoplasm. Table 1 shows few of the cases of glioma reported in literature of patients

Table 1: Glioma cases reported in literature of patients post treatment for acute lymphoblastic leukemia

Study	Age at diagnosis (Years)	Dose of radiation (Gray)	Latency (years)	Glioma histology
Walters et al, 1979	3	26.2	6	Astrocytoma
Salvati et al, 2008	10	24	22	Glioblastoma multiforme
Reiling et al, 1999	15.9	18	7	Glioblastoma multiforme
Joh et al, 2011	17	19.5	6	Glioblastoma multiforme
Brat et al, 1999	20	36	7	Anaplastic Astrocytoma
Salvati et al, 2008	26	24	26	Glioblastoma multiforme

post treatment for acute lymphoblastic leukemia.[5,6] Radiation induced gliomas tend to be of higher grade and show absence of somatic H3/IDH hotspot mutations.[5] The latency period from diagnosis of ALL to the onset of secondary glioma ranged from 1 to 26 years, with an average of 7.8 years. Our case had a latency period from the end of chemotherapy of 2 years and radiotherapy 5 years. The cumulative risk of secondary malignant brain tumors following treatment for ALL is 0.5–2.0% at 15 years and 4.91% at 30 years, which is a 10- to 20-fold greater risk than in age-matched controls.[7] The first fully documented case of CNS glioma following PCI for ALL was reported in 1979 by Walter's et al.[8] These tumors typically present in the pediatric population, have a characteristic substitution of methionine for lysine at residue 27 in either H3F3A or HIST1H3B/C genes or HIST1H3B/C genes,[9] generally occur in midline locations like thalamus, brainstem and spinal cord and so the role of surgery is primarily for diagnosis, owing to the surgical inaccessibility of most lesions. In our case, due to the lesion being in thalamic region, gross total resection (GTR) could not be done, so NTR was done. Data in adults is scarce, so treatment is based on extrapolation of results from the pediatric population. Chemotherapy has not shown any advantage over radiation alone but trials are ongoing to study a variety of chemotherapeutic agents.[10] These lesions are considered as high grade irrespective of histological features and location. Overall survival is typically 7–11 months in children and 8–19 months in adults.[10]

Conclusion

The diagnosis of H3K27 altered diffuse midline glioma in adults is itself rare and occurrence post chemotherapy and post PCI for treatment of ALL is very rare. Being highly aggressive malignancy, despite multimodality approach prognosis remains dismal at present.

References

1. Louis DN, Perry A, Wesseling P: The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro Oncology 2021; 23:1231-1251
2. Ostrom QT, Adel Fahmideh M, Cote DJ, et al: Risk factors for childhood and adult primary brain tumors. Neuro Oncology 2019; 21:1357-1375
3. Cahan WG, Woodard HQ, Higinbotham NL, Stewart FW, Coley BL: Sarcoma arising in irradiated bone: report of 11 cases. 1948 Cancer. 1998; 82:6-34
4. Schrantz JL, Araoz CA: Radiation induced meningeal fibrosarcoma. Archives of Pathology 1972; 93:26-31
5. Deng MY, Sturm D, Pfaff E, et al: Radiation-induced gliomas represent H3-/IDH-wild type pediatric gliomas with recurrent PDGFRA amplification and loss of CDKN2A/B. Nature Communications 2021; 12:5530
6. Yamanaka R, Hayano A: Secondary glioma following acute lymphocytic leukemia: therapeutic implications. Neurosurgical review 2017; 40:549-557
7. Hijiya N, Hudson MM, Lensing S, et al: Cumulative incidence of secondary neoplasms as a first event after childhood acute lymphoblastic leukemia. JAMA 2007; 297: 1207-1215
8. Walter AW, Hancock ML, Pui CH, et al: Secondary brain tumors in children treated for acute lymphoblastic leukemia at St Jude Children's Research Hospital. Journal of Clinical Oncology 1998; 16: 3761-3767
9. Vallero SG, Bertero L, Morana G, et al: Pediatric diffuse midline glioma H3K27- altered: A complex clinical and biological landscape behind a neatly defined tumor type. Frontiers in Oncology 2023; 12:1082062
10. Bin-Alamer O, Jimenez AE, Azad TD, Bettegowda C, Mukherjee D: H3K27M-Altered Diffuse Midline Gliomas Among Adult Patients: A Systematic Review of Clinical Features and Survival Analysis, World Neurosurgery 2022; 165:e251-e264