A Clinicopathological Analysis on Diffuse Midline Glioma in Adults

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Abstract

Purpose: Diffuse midline glioma (DMG), H3K27M mutant is a new entity that has become widely recognized. However, studies concerning DMG in adult patients remains rare. We did a retrospective study covering the largest amount of patients to date to analyze the clinicopathological characteristics of DMG in adult.

Methods: We reviewed 117 cases of adult DMG, collected their clinical and imaging data along with pathological results including H3K27M. Summarized their features and the connection with overall survival in different age groups.

Results: Among 117 cases, most tumors were located at the thalamus, 39 patients had H3K27M mutation, of whom 38 demonstrated down regulation of H3K27me3. The average overall survival of H3K27M-mutant gliomas was 13 months, while that of 78 H3K27M wild-type gliomas were 11.8 months. For young patients (age ≤ 35), The median survival time of the H3K27M-mutant was 20.1 months, while that of the H3K27M wild-type was 39.5 months. For older patients (age ≥ 35), the median survival time of the H3K27M-mutant was 22.3 months, while that of the H3K27M wild-type was 17.1 months. The OS of patients who received biopsies, subtotal resections, and total resections were 15.8, 17.6, and 11.6 months respectively.

Conclusion: The DMG in adults mainly occurred in the thalamus. H3K27M mutations tend to happen more frequently in young adults, and this genetic alteration results in a worse outcome only in young patients. For old patients, age and the approach of surgery are independent prognostic factors. Patients received biopsy instead of total resection had a better prognosis.

Introduction

The Diffuse Midline Glioma (DMG), H3K27M mutant, is a new pathologic entity that has become widely recognized since it was classified as a central nervous system neoplastic disorder by the WHO in 2016. As illustrated by its name, these gliomas are commonly located in midline structures of the brain, including the brainstem, thalamus, spinal cord, and cerebellum. These are defined as grade II gliomas, and are correlated with worse prognoses. However, with more and more investigations being carried out on this tumor entity, several questions have been noticed by researchers. Firstly, due to this kind of glioma mainly involving children, cases in adult patients are seldom reported and their prognoses remain unclear. Whether the H3K27M mutation still indicates a poor prognosis is questionable. Secondly, a successful neurosurgery to resect tumors in midline structures is a challenging task. As a result, the limitation on operations or genetic alterations that mainly contribute to the dismal outcome of DMG has been confused.

To figure out the prognosis of DMG in adult patients and explore the benefit that tumor resection offers patients, we have reviewed patients diagnosed with DMG in our hospital, collected their clinical and pathological data, and summarized its characteristics.
Methods And Materials

1. Study cohort

In this retrospective study, we reviewed our pathology database and picked out cases of patients diagnosed with glioma in the midline structures of their brains - including the thalamus, brainstem, medulla, and cerebellum - from January 2013 to December 2019. All the patients in our cohort were adults (age>18), and had to satisfy the following standards: 1. no previous medical history of glioma; 2. no severe complications during the perioperative period; 3. possess a complete medical history and have an accessible survival outcome. The tumor locations were verified by a radiologist through preoperative MR images. Pathologic sections were reassessed by two experienced pathologists according to the 2016 WHO classification of central nervous system tumors. To confirm the diagnosis, the H3K27M status were tested or reconfirmed via immunostain and PCR tests. All the tumor samples underwent genetic tests for IDH1/2. Other important markers including ATRX, P53, and Ki67 were all re-evaluated by immunohistochemistry.

Patients' detailed operation records were obtained by looking up our hospital's medical history system and by consulting the related neurosurgeons. The operation range was further confirmed from postoperative MR images. Patients were divided into 3 subgroups according to the range of tumor resection: biopsy, subtotal resection, and total resection.

2. Immunohistochemistry and PCR tests.

All the tumor specimens were formalin fixed and paraffin embedded (PFPE). Immunohistochemistry were performed on 4um sections with the antibodies: H3K27M (Leica Germany), H3K27me3 (Leica Germany), IDH (ZSGB-BIO China), ATRX (ZSGB-BIO China), P53 (ZSGB-BIO China), and Ki67 (Dako Denmark). For the PCR tests, DNA extractions were conducted with four 10mm sections from PFPE tissues. The enriched areas in tumor cells confirmed from HE sections were marked in advance. Tissues previously labeled for extraction were scraped off and placed on an Eppendorf tube for DNA isolation using the QIAamp DNA Mini Kit (Qiagen GmbH, Germany), the process for which was carried out according to the manufacturer's protocol. The spectrophotometer (Biophotometer Eppendorf, Germany) was used for detecting the quality and concentration of DNA samples.

The sequencing reactions were performed using clean-up exonuclease ExoSAP-IT (Affymetrix, Santa Clara, CA) via the Big Dye Terminator Cycle Sequencing Kit and capillary electrophoresis on the automated sequencer ABI3730 (Applied Biosystems, Carlsbad, CA). The PCR products were then analyzed and purified. Exonic alterations of sense and nonsense sequences were detected using SeqScape v2.5 software (Applied Biosystems), before being compared with the National Center for Biotechnology Information reference sequences.

3. Statistical analysis
We carried out the statistical analysis using the STATA software (Stata Corp TEXAS V15.1). The Kaplan-Meier estimator and Log-Rank test were conducted to form a comparison of patients’ survival rate in different subgroups. We also performed a COX model to evaluate the significance of related factors including age, sex, location, operation and genetic alterations. Pearson test was done to verify the correlation between age and H3K27M mutation. Independent T-tests were done to compare differences. The OS were defined and counted from the date of surgery to the date of death from any causes. This is viewed as statistically significant when \( p<0.05 \).

**Results**

1. Composition of patients

We identified 117 patients with DMG. They were all adults (>18 years old) ranging from 18 to 74 years old, with an average age of 43.7. We divided our cohorts into two subgroups depending on whether their age was ≥35, which formed the old group, or <35, which formed the young adult group. Of the total number of patients, 39 were classified as young adults, and 76 were put in the old group. 66 were males and 51 were females. Their pathological and clinical characteristics are summarized in Table-1. 88 tumors were located in the thalamus, 15 tumors were in the brainstem, while 8 were in the cerebellum and 6 were in the medulla [Fig-1]. Histologically, 20 corresponded to WHO grade II, 28 were grade III, and the remaining 69 cases were grade IV.

2. Immunohistochemistry and genetic findings

According to our IHC results, 39 patients were positive for H3K27M, and among these tumors, 38 demonstrated down regulation of H3K27me3 (38/39, 97.4%). Out of the tumors that were negative for H3K27M, 71 samples were diffusely positive for H3K27me3 (71/78, 91.0%) [Fig-2]. All tumor samples underwent PCR tests for H3.3 K27M, and all H3K27M immune-positive gliomas were genetically verified to be H3K27M mutants. Those which were H3K27me3 negative and H3K27M negative were confirmed to be H3K27M wild-type. The mutation rate of H3K27M in the thalamus, brainstem, medulla, and cerebellum were 31.1%, 50.0%, 25.0%, and 46.7% respectively. There were a total of 23 (23/39 59.0%) H3K27 mutant cases in the young adult group and 16 (16/76 21.1%) in the old group. Pearson tests demonstrated that there existed weak correlation between age and H3K27M mutation (\( r=0.394 \)). We also conducted routine IDH1/2 tests for all tumor specimens. Only 3 gliomas were mutated at R132H of IDH-1, and the rest were all IDH wild-type. The 3 IDH mutant gliomas were in the cerebellum (n=1) and brainstem (n=2), and were all H3K27M wild-type. In our cohort, 66 gliomas (56.4%) showed an overexpression of P53, and 33 (28.2%) gliomas had lost the expression of ATRX.

3. Treatment and overall survival

Out of all the patients, 18 received a total tumor resection and 6 patients underwent a subtotal tumor resection; 93 patients received a stereotactic biopsy instead of a tumor resection. All patients received chemotherapy with temozolomide accompanied by radiotherapy.
The mean follow-up time was 27 months (range from 7 to 68 months). Our patients' OS ranged from 2 months to 68 months with an average survival time of 15.2 months. The 1-year, 3-year survival rate were 70.2% and 18.7% respectively. The average survival time of the young adults was 16.2 months, while that of the older patients was 14 months, meaning that no statistical difference was observed ($p=0.244$). For 39 H3K27M mutant gliomas, the average overall survival was 13 months, while that of 78 H3K27M wild-type gliomas were 11.8 months. The average OS of 97 low grade gliomas (grade II) was 15.6 months and the average OS of 20 high grade gliomas (grade III and IV) was 15.1 months. It can therefore be seen that there is no statistical difference between the subgroups divided by H3K27M mutation ($p=0.85$) or histological grade ($p=0.35$). When dividing the data according to what operations they received, the OS of patients who received biopsies, subtotal resections, and total resections were 15.8, 17.6, and 11.6 months respectively. There is no statistical difference between the biopsy and subtotal resection groups, but the OS of patients who received a total resection was shorter than patients who didn't ($p=0.00$).

We then further explored the prognosis in different age groups. In younger patients, the clinicopathological factors mentioned above, including IHC markers, tumor grades, and operations have no influence on prognoses. The median survival time of the H3K27M-mutant was 20.1 months, while that of the H3K27M wild-type was 39.5 months. Patients with the H3K27M mutation had relatively worse prognoses than those without ($p=0.003$). For older patients, H3K27M is not a significant factor that affects patients' outcomes since the median survival time of the H3K27M-mutant was 22.3 months, while that of the H3K27M wild-type was 17.1 months ($p=0.460$). According to the COX analysis, the type of operation plays a key role in older patients. Those who received a biopsy had a better prognosis than those who received a total resection ($p=0.00$) [Fig-3].

**Discussion**

The "DMG, H3K27M mutant" is a newly defined entity in the 2016 revision of the WHO classification of CNS tumors. It is a high grade glioma which mainly occurs in children, and the mutation in H3.3G34 often results in a dismal outcome, with a median survival of around 1 year from the time of diagnosis in children$^2$. However, the characteristics of this tumor in adults remains unclear. We carried out a retrospective analysis on 117 adult patients which focused on their clinical and pathological characteristics and overall survival. To date, this is the largest cohort concerning DMG in adults in available literature.

Unlike pediatric patients whose midline gliomas are mostly located at the pons$^3$, our results revealed that the most common sites of DMG in adults are the thalamus and brainstem. For H3K27M wild-type gliomas, histologically low grade cases comprised more than H3K27M mutated gliomas. The average age of H3K27M-mutated glioma patients was obviously younger than H3K27M wild-type patients. According to our correlation analysis, there is a weak correlation between H3K27M mutations and the age of patients. All these factors prove that the H3K27M mutation tends to happen in younger patients among all age ranges. The older a patient is, the lower the chance they will develop a H3K27M mutation is.
Compared with the 6% rate of adult GBM and 14-29% rate of pediatric high grade glioma, the observed rate of ATRX mutation in our study was 23% and 36% in H3K27M mutated gliomas and H3K27M wild-type gliomas respectively. The ratio was higher than gliomas in non-midline structures, corresponding to the fact that H3K27M mutated gliomas seem to mainly result from lentheny of telomeres through ATRX mutation. Consistent with former reports, P53 overexpression was easily observed in our research, especially in the H3K27M mutated groups.

The H3K27M mutation is a genetic alteration reportedly linked with dismal outcomes in pediatric diffuse intrinsic pontine gliomas (DIPG). The same phenomenon was also founded in some study concerning H3K27M mutated DMG in adults. From 30 cases combined with the 171 cases reported in literature, Toshiyuki et al. found that the status of H3K27M is not related to the prognosis in patients who are older than 40. However, another research reported that H3K27M does not correlate with the prognoses of adults. To date, our study covers the most patients and found that H3K27M mutant gliomas tend to have poorer prognoses in patients younger than 35. For patients older than 35, the H3K27M mutation has no effect on the patients' outcomes. The contradictory results found in the literature is possibly due to some research not subdividing patients according to age. Our cohort's cutoff value for age was 35 instead of 40, which was used in the literature mentioned above. More cases are needed to discover the potential link between H3K27M and patients' age.

It is challenging for neurosurgeons to conduct operations on midline structures. The development of technologies - including the integration of functional mapping data on the neuro navigation cortical and subcortical electrical stimulation and awake anesthesia - has made surgical intervention more accepted as an important part of DMG treatment.

It is widely accepted that extensive resections of high grade gliomas is beneficial for patients, with more extensive resections providing added advantages. For adult DMG, it was reported that patients could benefit from tumor resections. Our work found that patients who underwent total tumor resections had a worse outcome than those who underwent a biopsy or subtotal resection. This was especially true for older patients, regardless of whether H3K27M had mutated or not. Our research was limited by the fact that we didn't include a quantitative analysis of the extent of resections, and we didn't take postoperative morbidity along with life quality into consideration. However, this tells us that unnecessary total tumor resections is a potential factor that can lead to poor overall survival. Biopsies are recommended so that the genetic phenotype can be accurately decided. A more comprehensive study about the effect of operation is therefore needed.

With regards to pediatric DMG, the WHO histological grade is of no prognostic significance. From our observations of adult patients, the tumor grade has no influence on the prognosis either. This may be partially due to that most specimen were obtained by biopsy, which added the possibility of sample error.

It is interesting of the H3K27M mutation's low frequency and meaninglessness on old patients. Due to the limited tumor samples available, we weren't able to explore other genetic changes. Further studies with...
complete genetic records are needed to describe the characteristics of this kind of glioma and potentially obtain a more comprehensive understanding of the gene, H3K27M.

In conclusion, this study covers the largest single-center series of adult DMG patients. It found that the DMG in adults mainly occurred in the thalamus. H3K27M mutations tend to happen more frequently in young adults (age<35), and this genetic alteration results in a worse outcome only in young patients. For old patients, age and the approach of surgery are independent prognostic factors. Patients received biopsy instead of total resection had a better prognosis. Histological grade, tumor location and H3K27M mutation has no prognostic value.

**Declarations**

**Funding**

No funding was received for conducting this study.

**Conflict of interest**

The authors have no conflicts of interest to declare that are relevant to the content of this article.

**Data availability**

All data used during the study are available from the corresponding author by request.

**Ethical approval**

The study was approved by the research ethics committee of HuaShan Hospital affiliated to FuDan University.

**Contributions**

Study conception and design are mainly contributed by Xiong Ji and Tang Feng. Material preparation, data collection and analysis were performed by Nie Xiao yu, Hu Xiao mu and Xu Kai lun. The first draft of the manuscript was written by Hu Xiao mu and Xu Kai lun, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**References**

[1] Louis DN, Perry A, Reifenberger G, von Deimling A, Figarella-Branger D, Cavenee WK, Ohgaki H, Wiestler OD, Kleihues P, Ellison DW: The 2016 World Health Organization Classification of Tumors of the Central Nervous System: a summary. Acta Neuropathol 2016, 131:803-20.

[2] Lowe BR, Maxham LA, Hamey JJ, Wilkins MR, Partridge JF: Histone H3 Mutations: An Updated View of Their Role in Chromatin Deregulation and Cancer. Cancers (Basel) 2019, 11.
[3] Solomon DA, Wood MD, Tihan T, Bollen AW, Gupta N, Phillips JJ, Perry A: Diffuse Midline Gliomas with Histone H3-K27M Mutation: A Series of 47 Cases Assessing the Spectrum of Morphologic Variation and Associated Genetic Alterations. Brain Pathol 2016, 26:569-80.

[4] Brennan CW, Verhaak RG, McKenna A, Campos B, Noushmehr H, Salama SR, Zheng S, Chakravarty D, Sanborn JZ, Berman SH, Beroukhim R, Bernard B, Wu CJ, Genovese G, Shmulevich I, Barnholtz-Sloan J, Zou L, Vegalas R, Shukla SA, Ciriello G, Yung WK, Zhang W, Sougnez C, Mikkelsen T, Aldape K, Bigner DD, Van Meir EG, Prados M, Sloan A, Black KL, Eschbacher J, Finocchiaro G, Friedman W, Andrews DW, Guha A, Iacocca M, O'Neill BP, Foltz G, Myers J, Weisenberger DJ, Penny R, Kucherlapati R, Perou CM, Hayes DN, Gibbs R, Marra M, Mills GB, Lander E, Spellman P, Wilson R, Sander C, Weinstein J, Meyerson M, Gabriel S, Laird PW, Haussler D, Getz G, Chin L, Network TR: The somatic genomic landscape of glioblastoma. Cell 2013, 155:462-77.

[5] Schwartzentruber J, Korshunov A, Liu XY, Jones DT, Pfaff E, Jacob K, Sturm D, Fontebasso AM, Quang DA, Tonjes M, Hovestadt V, Albrecht S, Kool M, Nantel A, Konermann C, Lindroth A, Jager N, Rausch T, Ryzhova M, Korbel JO, Hielscher T, Hauser P, Garami M, Klekner A, Bognar L, Ebinger M, Schuhmann MU, Scheurlen W, Pekrun A, Fuhlold MC, Roggendorf W, Kramm C, Durken M, Atkinson J, Lepage P, Montpetit A, Zakrzewska M, Zakrzewski K, Liberski PP, Dong Z, Siegel P, Kulozik AE, Zapatka M, Guha A, Malkin D, Felsberg J, Reifenberger G, von Deimling A, Ichimura K, Collins VP, Witt H, Milde T, Witt O, Zhang C, Castelo-Branco P, Lichter P, Faury D, Tabori U, Pla C, Majewski J, Pfister SM, Jabado N: Driver mutations in histone H3.3 and chromatin remodelling genes in paediatric glioblastoma. Nature 2012, 482:226-31.

[6] Sturm D, Bender S, Jones DT, Lichter P, Grill J, Becher O, Hawkins C, Majewski J, Jones C, Costello JF, Iavarone A, Aldape K, Brennan CW, Jabado N, Pfister SM: Paediatric and adult glioblastoma: multiform (epi)genomic culprits emerge. Nat Rev Cancer 2014, 14:92-107.

[7] Aihara K, Mukasa A, Gotoh K, Saito K, Nagae G, Tsuji S, Tatsuno K, Yamamoto S, Takayanagi S, Narita Y, Shibui S, Aburatani H, Saito N: H3F3A K27M mutations in thalamic gliomas from young adult patients. Neuro Oncol 2014, 16:140-6.

[8] Castel D, Philippe C, Calmon R, Le Dret L, Truffaux N, Boddaert N, Pages M, Taylor KR, Saulnier P, Lacroix L, Mackay A, Jones C, Sainte-Rose C, Blauwblomme T, Andreiolo F, Puget S, Grill J, Varlet P, Debily MA: Histone H3F3A and HIST1H3B K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes. Acta Neuropathol 2015, 130:815-27.

[9] Meyronet D, Esteban-Mader M, Bonnet C, Joly MO, Uro-Coste E, Amiel-Benuaicha A, Forest F, Rousselot-Denis C, Burel-Vandenbos F, Bourg V, Guyotat J, Fenouilt T, Jouvet A, Honnorat J, Ducray F: Characteristics of H3 K27M-mutant gliomas in adults. Neuro Oncol 2017, 19:1127-34.

[10] Liu Y, Zhang Y, Hua W, Li Z, Wu B, Liu W: Clinical and Molecular Characteristics of Thalamic Gliomas: Retrospective Report of 26 Cases. World Neurosurg 2019, 126:e1169-e82.
[11] Enomoto T, Aoki M, Hamasaki M, Abe H, Nonaka M, Inoue T, Nabeshima K: Midline Glioma in Adults: Clinicopathological, Genetic, and Epigenetic Analysis. Neurol Med Chir (Tokyo) 2020, 60:136-46.

[12] Ebrahimi A, Skardelly M, Schuhmann MU, Ebinger M, Reuss D, Neumann M, Tabatabai G, Kohlhof-Meinecke P, Schittenhelm J: High frequency of H3 K27M mutations in adult midline gliomas. J Cancer Res Clin Oncol 2019, 145:839-50.

[13] Alemo S, Sayadipour A: Role of intraoperative neurophysiologic monitoring in lumbosacral spine fusion and instrumentation: a retrospective study. World Neurosurg 2010, 73:72-6; discussion e7.

[14] De Witt Hamer PC, Robles SG, Zwinderman AH, Duffau H, Berger MS: Impact of intraoperative stimulation brain mapping on glioma surgery outcome: a meta-analysis. J Clin Oncol 2012, 30:2559-65.

[15] Tang S, Liao J, Long Y: Comparative assessment of the efficacy of gross total versus subtotal total resection in patients with glioma: A meta-analysis. Int J Surg 2019, 63:90-7.

[16] Wu B, Tang C, Wang Y, Li Z, Hu S, Hua W, Li W, Huang S, Ma J, Zhang Y: High-grade thalamic gliomas: Microsurgical treatment and prognosis analysis. J Clin Neurosci 2018, 49:56-61.

[17] Dey M, Lin Y, Melkonian S, Lam S: Prognostic factors and survival in primary adult high grade brainstem astrocytoma: a population based study from 1973-2008. J Clin Neurosci 2014, 21:1298-303.

[18] Cohen KJ, Jabado N, Grill J: Diffuse intrinsic pontine gliomas-current management and new biologic insights. Is there a glimmer of hope? Neuro Oncol 2017, 19:1025-34.

Tables

**Table 1** Clinical and pathological characteristics of the patients with gliomas in midline location
| Epidemiology | H3K27M-Wild (N=78) | H3K27M-mutant (N=39) | P-value |
|--------------|-------------------|---------------------|---------|
| Sex          |                   |                     |         |
| M            | 41                | 25                  | 0.323   |
| F            | 37                | 14                  |         |
| Age ≥35      | 16                | 23                  | 0.000   |
| Location     |                   |                     | 0.082   |
| Brainstem    | 7                 | 8                   |         |
| Thalamus     | 62                | 26                  |         |
| Cerebellum   | 6                 | 2                   |         |
| Medulla      | 3                 | 3                   |         |
| Pathology    |                   |                     |         |
| WHO Histology Grading |       |                     | 0.048   |
| II           | 17                | 3                   |         |
| ≥III+IV      | 61                | 36                  |         |
| IDH Mutation |                   |                     | 0.550   |
| Yes          | 3                 | 0                   |         |
| No           | 75                | 39                  |         |
| ATRX Mutation|                   |                     | 0.087   |
| Yes          | 60                | 24                  |         |
| No           | 18                | 15                  |         |
| P53 Overexpression |         |                     | 0.323   |
| Yes          | 41                | 25                  |         |
| No           | 37                | 14                  |         |
| H3K27Me3 Downregulation |     |                     | 0.000   |
| Yes          | 7                 | 38                  |         |
| No           | 71                | 1                   |         |
Surgical resection

Biopsy

Subtotal resection  60  33
Total resection  2  4

Overall Survival

|        | Young (M) | Old (M) |
|--------|-----------|---------|
| Overall Survival | 16  2   |         |
| Young (M)         | 39.5   | 17.1    |
| Old (M)           | 20.1   | 22.3    |

P = 0.010  
P = 0.465

Y: years, M: months

Figures

Figure 1

The age and location distribution of tumor in our research.
Figure 2

The histological image and immunohistochemistry results of H3K27M and H3K27me3, A1-A3: a histologically grade II glioma showing H3K27M expression\textsuperscript{A2} and downregulation of H3K27me3\textsuperscript{A3}; B1-B3: a histologically grade III glioma showing H3K27M expression\textsuperscript{B2} and no downregulation of H3K27me3\textsuperscript{B3}; C1-C3: a histologically grade IV glioma showing H3K27M expression\textsuperscript{C2} and loss the expression of H3K27me3\textsuperscript{C3}.
Figure 3

Relationship between clinicopathological factors and OS: A, relationship between H3K27M and OS in young patients, the H3K27M mutant had a worse prognosis; B, relationship between H3K27M and OS in old patients, there is no difference in prognosis of two different subgroups; C-D, relationship between histological grade and OS in young and old patients, the low grade group means WHO grade II and the high grade group includes WHO grade III and IV. There is no difference in different histological grades; E, relationship between operation and OS in young patients, although there was no statistical difference, the OS of biopsy was better than other two groups; F, relationship between operation and OS in old patients, only 1 patient received subtotal resection, the OS of biopsy is better than that of total resection.