

## CNS Gliosis not Neoplasia in Kabuki Syndrome: A Case Report of a Brain ‘Tumor’

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**Citation:** Honey CM, Cheng J, Sulistyanto A, Heran MKS, Schutz P, et al. (2020) CNS Gliosis not Neoplasia in Kabuki Syndrome: A Case Report of a Brain ‘Tumor’. *J Neurol Neurol Disord* 6(1): 104

### Abstract

An eight-year-old boy with Kabuki Syndrome (KS) and an enlarging CNS mass is presented. The ‘tumor’ was discovered incidentally during MR imaging for a behavioral disorder and was located within the left globus pallidus. Retrospective review of previous MRIs showed no abnormality in the basal ganglia seven years earlier but a small region (a few pixels) of increased in T2 signal intensity three years earlier. The lesion exhibited no mass effect or surrounding edema on imaging and produced no obvious clinical effects that could be discerned beyond his abnormal baseline due to the other CNS manifestations of KS. Laboratory investigations revealed borderline elevated serum beta hCG and alpha-1 fetoprotein. Stereotactic biopsy of the basal ganglia mass was performed without complication. Immunohistochemical staining revealed gliosis and mild inflammatory changes without evidence of neoplasia within the core and at the edge of the lesion. Over the following year, the patient has remained clinically stable and MR imaging showed no further growth of the gliotic mass. Recognition of this potential pathology in Kabuki syndrome may guide clinicians to serial imaging rather than biopsy.

**Keywords:** Kabuki Syndrome; CNS Tumor; Basal Ganglia; Pediatric Neurosurgery

### Introduction

Kabuki syndrome (KS) is a rare genetic disorder first described in 1981 and is characterized by distinctive facial dysmorphism, skeletal abnormalities and cognitive impairment [1,2]. Although the diagnosis of KS can be made clinically based on facial dysmorphism alone,<sup>3</sup> the condition has a genetic etiology and has been associated with several mutations including duplication in chromosome 8p22-8p23.1, mutation in the *KMT2D* (also known as *MLL2*) gene at 12q13.12 and the more recently discovered *KDM6A* gene at Xp11.3 [4-6]. Over 350 sporadic cases have been documented in literature describing the various less common systemic manifestations of this condition including ophthalmologic, cardiac, renal and gastrointestinal, endocrine and neurologic abnormalities [6]. KS is frequently described in literature with central nervous system (CNS) manifestations, most commonly cognitive impairment with cerebral atrophy, CNS malformations and seizures [3,5,7]. There are two case reports of arachnoid cysts but no previous documentation of CNS neoplasia in these patients [6,9].

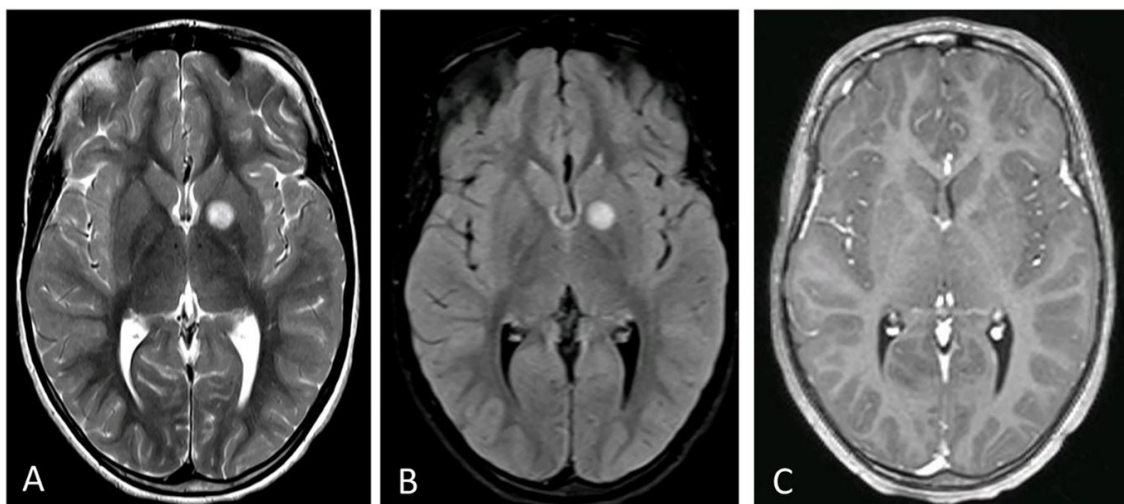
We report an 8-year-old boy with KS presenting with an asymptomatic 10 mm spherical lesion within the anterior left globus pallidus. The lesion had enlarged over three years but follow-up imaging showed no growth over the subsequent eight months. All laboratory investigations were negative except for mildly elevated CSF beta hCG and serum AFP on two occasions. A stereotactic biopsy of the basal ganglia was performed without complication. The biopsy revealed gliosis with no neoplasia. Follow-up over the next year showed no growth on imaging and no changes in clinical examination except for improvements in language, motor and social development. This is the first case, to our knowledge, of a CNS mass reported in Kabuki syndrome. Recognition of this pathology may guide clinicians to consider a more conservative non-surgical approach for future patients.

## Case Report

### History

This 8-year old boy presented with an asymptomatic brain mass within the left globus pallidus found incidentally on magnetic resonance imaging. He denied headache and his parents reported no recent changes in his physical functioning or behavior. Review of previous MR imaging showed no abnormality in the area seven years earlier but subtle T2 signal changes three years earlier. He had a heterozygous MLL2 mutation (p.C142s) resulting in multiple comorbidities associated with the clinical phenotype of Kabuki syndrome including global developmental delay, autism spectrum disorder, attention deficit hyperactive disorder, microcephaly, retinal dystrophy, strabismus, diffuse osteopenia and characteristic facial dysmorphism with bitemporal narrowing, elongated palpebral fissures with epicanthal fold, broad high-ridged nose and high-arched palate.

The presenting MRI showed a hyperintense 10 mm spherical lesion within the left globus pallidus on T2 and FLAIR sequences (Figure 1A and 1B) with mild hypointensity and no enhancement following Gadolinium on T1 sequences (Figure 1C). Retrospective review of an MRI performed three years earlier demonstrated a very small T2 signal change in the same area. Follow-up imaging eight months after the presenting MRI, showed no further growth of the lesion. There was no peri-lesional edema or mass effect. Laboratory investigations following the presenting MRI were negative except for borderline elevated serum Alpha-1-Fetoprotein (AFP) at 8.5 ug/L (normal <8 ug/L). The beta human chorionic gonadotropin (hCG) tumor marker was undetectable (normal <2 IU/L). Repeat testing five months later showed AFP = 11 ug/L and b-hCG 2.8 IU/L. This raised the possibility of a germ cell tumor and prompted neurosurgical biopsy for definitive diagnosis. The differential diagnosis at the time of biopsy was germ cell tumor or low-grade glioma.



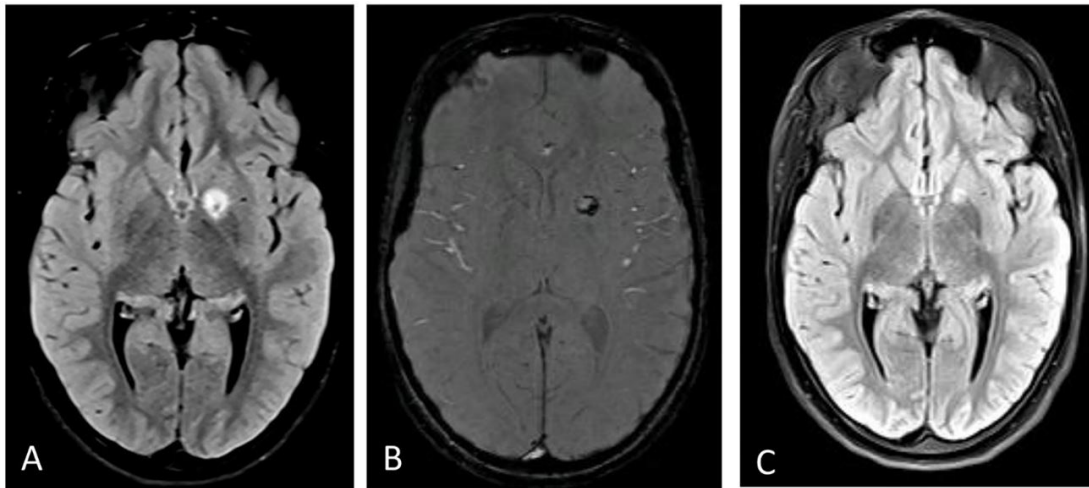
**Figure 1:** MRI of lesion: (A) The presenting MRI showed a hyperintense 10 mm spherical lesion within the left globus pallidus on T2; (B) and FLAIR; (C) Sequences with mild hypointensity and no enhancement following Gadolinium on T1 sequences

### Examination

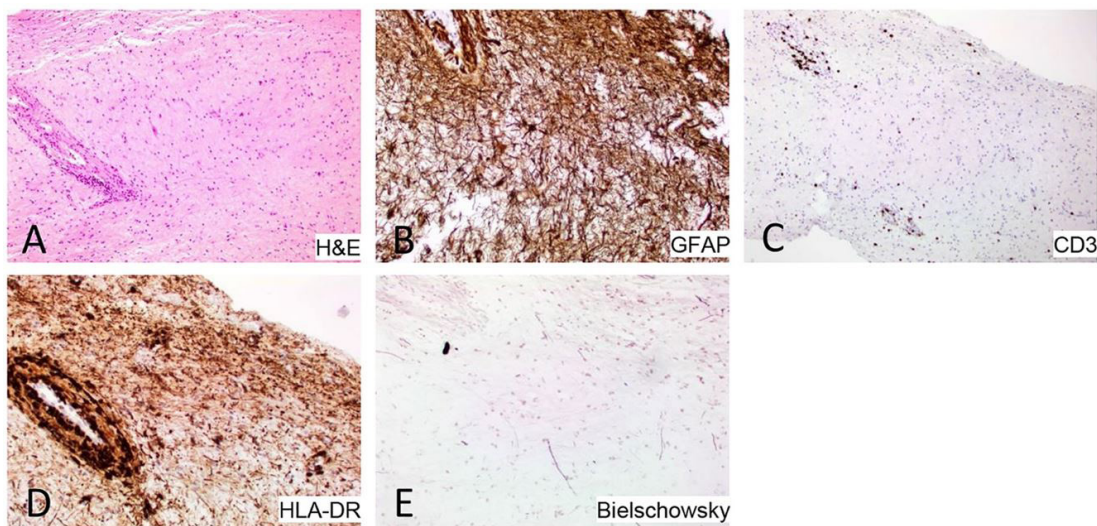
On examination, this 128 cm, 25 kg boy looked well with no suggestion of infection or systemic illness. Compared with previous neurological examinations, he had no new findings of contralateral weakness, incoordination or movement disorder. His baseline examination was abnormal because of his Kabuki Syndrome. He had a wide-based, out-toeing gait, uncoordinated running, and inability to tandem walk which had been present following earlier orthopedic surgeries. He had longstanding developmental delay in language, social and motor skills. Testicular exam and ultrasound were normal and he had no signs of precocious puberty.

### Operation

The patient underwent a frame-based MRI-guided brain biopsy under general anesthetic without complication. Pre-operative imaging included T2-weighted scans to delineate the target and post Gadolinium T1-weighted scans to select the trajectory and avoid intracranial vessels. There was no obvious necrotic core or circumferential enhancement so the biopsy targets were chosen in the centre of the lesion and at its superolateral edge. The entry was made through the middle frontal gyrus and the resistance of the needle was slightly increased at the brain-tumor interface. Two core Biopsies (1.0 x 0.2 x 0.2 cm) were taken at each target. The patient was discharged home the following day. Following the biopsy results, a repeat MRI was performed one week later to confirm biopsy site (Figures 2 and 3).



**Figure 2:** Post-operative MRI; Following the unexpected biopsy results, a repeat MRI was performed one week later to confirm the biopsy site. The FLAIR sequence; (A) shows a punctate hole in the middle of the lesion where the biopsy was taken and the GRE sequence; (B) shows a small, asymptomatic hemorrhage at the region of the upper border of the lesion. One-year post-operative the FLAIR sequence; (C) showed no growth of the lesion



**Figure 3:** Neuropathology; The biopsy showed abnormal gliotic appearing tissue; (A-E) likely from the area of globus pallidus with adjacent more normal tissue with pencil fibres of Wilson indicating putamen (not shown); On haematoxylin and eosin stained sections: (A) There is loss of neurons and rarefaction with coarseness of neuropil. GFAP immunohistochemistry; (B) highlights the coarse fibrillarity. There are a few perivascular and rare parenchymal T-cells on CD3 immunohistochemistry; (C) B-cells were not identified on CD20 immunohistochemistry (not shown). HLA-DR labelled sections demonstrate significant microglial activation and perivascular macrophages; (D) While Bielschowsky silver impregnation highlights a loss of axons in the neuropil; (E): to some extent in keeping with neuronal loss seen on H&E

## Histopathological Findings

Immunohistochemical staining of the biopsies demonstrate basal ganglia tissue with mild inflammatory change and chronic gliosis of unknown etiology with a mild perivascular lymphocytic T-cell infiltrate and microglial activation (Figure 3). There was no suggestion of neoplasia. The main differential diagnosis for the changes observed are 1) a primary inflammatory process, such as an autoimmune or infectious process and/or 2) etiologies causing primarily gliosis with a secondary inflammatory component.

## Discussion

Although patients with Kabuki Syndrome have a high incidence of CNS manifestations, the majority of cases described in literature are associated with atrophic processes and none with neoplasia [3,7,8]. Two cases of arachnoid cysts have been reported in association with KS [7,9]. The diagnosis of gliosis in KS is also rare. One case of a 21-year-old man with KS developed unilateral prepaillary gliosis in the retina [10]. A second case of a 1-year-old girl with Zellweger spectrum disorder (a Kabuki-like phenotype with similar dysmorphic facial features) was reported to have 'nonspecific gliosis at subcortical and periventricular deep white matter' on MRI [11]. These MRI findings were diffuse and not circumscribed like our case. That latter case was associated with a Peroxisomal Biogenesis Factor 1 (*PEX1*) gene mutation at chromosome 7q21-22 which regulates peroxisome activity [11]. Mutations in that gene can cause progressive leukoencephalopathy affecting white matter including the corpus callosum and brainstem [11].

Based on our histopathological studies, the main differential diagnosis for the gliotic changes observed were 1) a primary inflammatory process, such as an autoimmune or infectious process and/or 2) a primarily gliosis with a secondary inflammatory component. KS is frequently associated with autoimmunity and impaired immune response leading to deficiency in various classes of antibodies (hypogammaglobulinemia) [12,13]. It is therefore possible that our patient developed the lesion following a subclinical infectious process. All tests for infection, including *Bartonella* serology, have been negative.

The borderline elevated AFP and beta hCG were likely spurious in retrospect as our laboratory had recently switched to a new assay and duplicate samples sent to a second laboratory were reported to be within normal limits.

## Conclusion

We report the first case, to our knowledge, of a brain mass in a patient with Kabuki Syndrome. The histopathology was gliosis with no evidence of neoplasia. The neuroimaging was consistent with a benign process with no perilesional edema, no enhancement, and no significant mass effect. The clinical significance of this case report is that recognition of this potential pathology may guide future clinicians to a more conservative non-surgical management.

## Disclosure

The authors report no conflict of interest concerning the materials or methods used in this study or the findings reported in this paper.

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