

The Dilemma of Multifocality in Insular Tumors: Multicentricity versus Metastasis

Abstract

Background and Purpose: Multifocality and metastasis from insular glioma are extremely rare. Pathological insights and elaboration of the clinical course of this condition will contribute to their better understanding. **Materials and Methods:** Among 123 consecutively operated insular gliomas, 5 patients (4.2%) presented with a multifocal tumor. The clinico-radiological, histo-molecular, and treatment outcomes were noted and compared with the unifocal insular glioma cohort. **Results:** Among the five patients, all were males and involved the right insular lobe. Three patients presented with synchronous tumors, while two patients developed metachronous multifocal tumors. The histology of the insular tumor was Grade I glioma in 1, Grade II astrocytoma with p53 mutation in 2, and anaplastic astrocytoma and glioblastoma in one patient each. Histological confirmation of the second lesion was performed in two patients, showing the same histology of the insular tumor. Interconnection between the tumors was apparent through cerebrospinal fluid pathways in four patients, while no such connection could be established in one patient. Barring the patient of Grade I glioma, the rest of the patients died within months of the diagnosis. **Conclusion:** Multifocal insular glioma is rare and probably represents a biologically more aggressive tumor. Insular glioma that touches the ventricle appears a common denominator for multifocality. True multicentricity is rare. The prognosis in insular glioma with multifocality is poor in non-Grade I gliomas.

Keywords: Cerebrospinal fluid spread, insular glioma, multicentric, radiotherapy, surgery

Introduction

Insular gliomas are challenging tumors. Our understanding of these tumors has improved immensely, both on a conceptual and technological front.^[1-4] Multifocality and possible tumor metastasis from insular glioma are extremely rare and less explored.^[5] Therefore, very little is known regarding the predictability of such growth patterns and their management implications. Multifocal gliomas are rare and unique entities. They constitute 8%–10% of all gliomas.^[6,7] The inherent complexity of insular gliomas gets accentuated in the setting of additional multifocality. In this article, the authors highlight multifocality in insular gliomas and share the learning points with five such cases encountered in their experience.

Materials and Methods

We reviewed our experience with insular gliomas over 10 years (2010–2020) for multifocal tumors in the setting of insular

gliomas. We included insular gliomas with multifocality detected at the same presentation (synchronous tumors) and those presenting subsequently after insular glioma surgery (metachronous).

The clinical, imaging, surgical, histo-molecular markers and outcome were assessed in the multifocal tumors and compared with the remaining tumor which did not have multifocality.

Results

We operated on 123 cases of insular glioma over 10 years. Out of these, we found multifocality in 5 patients (4.0%). The key features of these cases are presented in Table 1.

Characteristics of the insular tumor

All five patients had right insular lobe involvement. All except one patient (patient #5) were young adults, and all were males [Table 1]. The tumor was confined to the insula in three patients [Yasargil type 3A, Figures 1-3], and the

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Table 1: Details of multifocal insular glioma in the series

Age/ gender	Clinical presentation	Radiological characteristics of insular tumor	Radiological characteristics of the second tumor	Treatment	Histology and molecular profile	Outcome
27/male	Synchronous Headache × 1 year Generalized seizures × 1 year	Right insular mass enhancement + Yasargil type 3A [Figure 1]	Single-enhancing lesion involving the occipital horns and splenium of the corpus callosum	Insular tumor: Near-total excision Second tumor: Observation No adjuvant therapy	Grade III astrocytoma (molecular markers were not done)	Discharged intact; died after a month from unknown cause (survival 1 month)
25/male	Synchronous Left-sided focal seizures × 5 years	Right insular mass Patchy enhancement Yasargil type 5B [Figure 2]	Single left cerebellar mass no enhancement	Insular tumor: Near-total excision Second tumor: Observation	DNET IDH negative p53 not done	Pt doing well and alive after 3 years without much growth of cerebellar tumor
22/male	Metachronous First presentation: Diplopia × 2 months Seizures × 2 months Second presentation: Cerebellar ataxia after 2 years	Right insular mass Patchy enhancement Yasargil type 5B [Figure 3]	Single midline cerebellar mass No enhancement	Insular tumor: Subtotal tumor excision Cerebellar tumor: Midline suboccipital craniotomy and tumor decompression	Insular tumor: Astrocytoma (WHO Grade II), IDH mutated, P53 positive Cerebellar tumor: Astrocytoma (WHO Grade II), IDH: Negative, p53 positive	Survival: 2.5 years Survival after metachronous tumor detection: 3 months
45/male	Metachronous First presentation: Seizures × 2 years Second presentation: Generalized weakness in all 4 limbs × 1 month Altered sensorium × 7 days	Right insular mass No enhancement Yasargil type 3A [Figure 4]	Multiple contrast-enhancing lesions in the right temporal and parietal lobe and left peritrigonal region	Insular tumor: Near-total excision Second tumor: Observation Adjuvant therapy taken	Completed chemoradiotherapy Astrocytoma (WHO Grade II), IDH mutated, P53 positive	OS: 2 years Survival after metachronous tumor detection: 2 months
63/male	Synchronous Urinary incontinence × 2 months Left hemiparesis × 1 month	Right insular mass heterogeneous enhancement, Yasargil type 3A [Figure 5]	Single right posterior frontal lesion with heterogeneous enhancement	Insular tumor: Near-total excision Second tumor: Subtotal excision Did not take chemoradiotherapy	Glioblastoma (WHO Grade IV) IDH negative P53 negative	OS: 2 months

DNET – Dysembryoplastic neuroepithelial tumor; OS – Overall survival; IDH – Isocitrate dehydrogenase

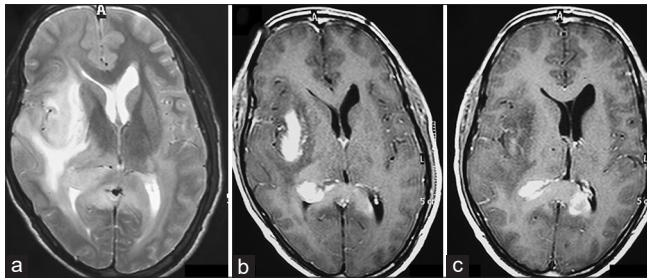


Figure 1: Magnetic resonance T2 (a) and contrast-enhanced (b and c) axial images depict the right insular mass with heterogeneous enhancement, confined within the insula (Yasargil type 3A). Contrast-enhancing lesions involving the bilateral occipital horns and splenium of the corpus callosum can be appreciated (b and c)

other two patients had insulo-opercular tumors [Yasargil type 5B, Figures 4 and 5] with tumor extension into the ventricle in two patients [Figures 4 and 5]. Histopathologically, we had one patient with Grade I glioma (dysembryoplastic neuroepithelial tumor [DNET]), two patients with Grade 2 astrocytoma (2 isocitrate dehydrogenase [IDH] mutant, 1 wild type), one anaplastic astrocytoma (IDH mutation could not be tested), and one glioblastoma (IDH wild type). p53 mutation was positive in both patients with both Grade II astrocytoma, absent in 1, while not performed in one patient.

Characteristics of the second tumor

All patients had a single second tumor. The involvement was midline (patient #3) and left paramedian (patient #2), both being around the fourth ventricle. Two patients (patient #1 and patient #4) had intraventricular tumor deposits lining the dependent parts. The patient with insular glioblastoma had an ipsilateral premotor cortex lesion (case #5).

The second lesion was synchronous in 3 patients (cases # 1, 2, and 5), while it appeared metachronously within 2 years with a new onset of symptoms in patients #3 and 4. Histopathological analysis of the second lesion was available in two cases, and it revealed the same characteristics of the primary tumor (patients #3 and 5). In patient #4, the secondary lesion showed a postcontrast enhancement indicating that the lesion was probably of a higher grade. Imaging in the rest of the cases showed characteristics precisely similar to the insular tumor.

Management and outcome

All the patients underwent surgical excision of the insular tumor. The surgical approach was either trans-sylvian (patients #1, 4, and 5) or transcortical (patients #2 and 3), as per the tumor's extension.^[2,8,9] The extent of excision is shown in Table 1. In one patient (case #5), simultaneous excision (subtotal) of the second lesion was performed using the same craniotomy. In patient #3, the posterior fossa tumor was subtotally excised in a separate surgery. We pursued a policy of observation in case #2, and the lesion has remained stable during follow-up. The

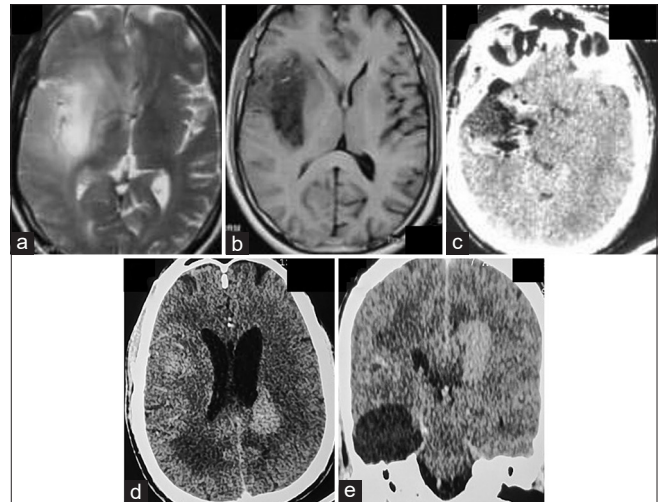


Figure 2: T2 and contrast magnetic resonance axial images (a and b) show the right insular mass with no enhancement, Yasargil type 3A. Immediate postoperative computed tomography images (c) suggest a surgical cavity of anteromedial temporal resection combined with the tumor excision. Follow-up computed tomography scans done after 1 year at new-onset symptoms suggested a contralateral occipital horn hyperdense tumor mass (d and e)

other two patients (#1 and #4) did not undergo surgery and died at follow-up. Patient #1 was advised chemoradiation, discharged in a stable condition, but expired from unknown cause after a month. While patient #4 presented in altered sensorium and after discussing the prognosis, they refused treatment and the patient subsequently expired within a month. Patient #2 was not advised any chemoradiation due to a Grade I tumor histology, and he is currently under follow-up. Patient #3, having undergone a subtotal excision, received radio-chemotherapy after the first surgery. He expired after 2 months of surgery for the posterior fossa tumor. Patient #5 also expired after 1 month, before adjuvant chemoradiation.

Table 2 shows the differences between the multifocal insular gliomas and the unifocal tumors operated during the same time. Exclusive involvement of males and right insular involvement were distinctive features of multifocal insular glioma. Moreover, multifocal tumors were more common in younger patients. The frequency of p53 mutation was higher in multifocal Grade II astrocytomas.

Discussion

In this series, we have presented five examples of insular glioma of various grades associated with a second glioma appearance at a different site. Through these examples, we want to discuss the issue of multifocality in the setting of insular involvement. We aim to discuss the possible pathogenetic mechanisms for such growth patterns.

Incidence and definitions

Multifocal gliomas constitute around 8%–10% of all gliomas.^[6,7] Their incidence with insular gliomas is

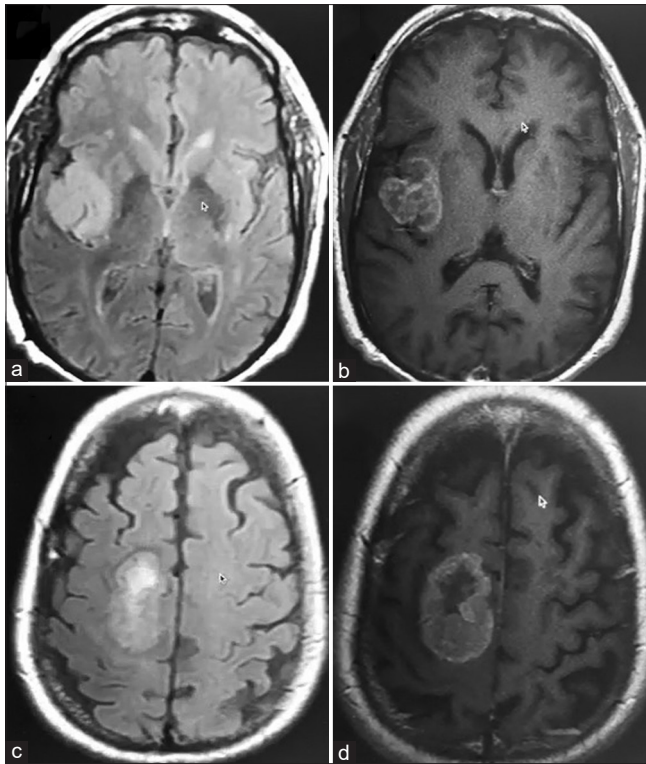


Figure 3: T2 and contrast axial (a and b) magnetic resonance images showed an enhancing, irregularly margined right insular mass with heterogeneous enhancement, Yasargil type 3A. Simultaneously, a single (c and d) right posterior frontal lesion (in front of the motor cortex) with heterogeneous enhancement was seen without any interconnecting tissues

Table 2: Basic differences between unifocal (*n*=118) and multifocal insular gliomas (*n*=5) in our series

Parameters	Unifocal (<i>n</i> =118)	Multifocal (<i>n</i> =5)
Median age (years)	35.5	27
Gender	Male=78, female=40	Male=5
Side	Right=58, left=60	Right=5
Grade	Grade I=3	Grade I=1
	Grade II=66	Grade II=2
	Grade III=23	Grade III=1
	Grade IV=26	Grade IV=1
P53 status in Grade II astrocytoma, <i>n</i> (%)	Positive=9 (45)*	Positive=2 (100)

*Available in 20 patients with Grade II astrocytoma

probably much lower, as we saw (4%). Our previous publication on multifocal glioblastomas has pointed out the differences between the two categories and pointed out their poorer outcomes.^[10] There is often a tendency to confuse them with brain metastasis from an unknown primary,^[3,11,12] leading to underestimating these lesions' true incidence.

Historically, several authors have tried to distinguish between multifocal and multicentric gliomas.^[13,14] Multifocal gliomas are in anatomical continuity (described as collision tumors), or a connection through a known white matter path can be established between them.^[15-17] On the other hand,

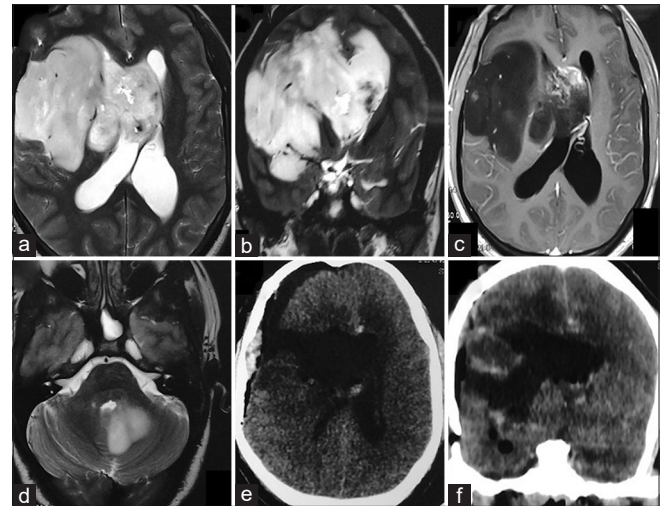


Figure 4: Magnetic resonance T2 axial (a), coronal (b) images show a large heterointense right insular mass lesion extending into the lateral ventricle with the patchy enhancement of the ventricular part (c). The lesion corresponds to Yasargil type 5B. (d) A single left cerebellar mass lesion, it did not enhance. (e and f) The postoperative computed tomography images showing near-total excision of the insular tumor. The cerebellar tumor was observed

multicentric gliomas are located at a distance geographically, and no anatomical pathway connects them (e.g., patient #5 in our series). These demarcations, however, have faded over time, and both conditions are treated identically with similar outcomes. Nevertheless, we saw both varieties in our series, and we believe that the underlying mechanisms may be different in both.

Pathology and pathogenesis

These tumors are common in the setting of a family history of malignancies or the background of some other malignancies in the patient.^[18-20] P53 mutation is detected in a very high number of these patients.^[6] In addition, a higher incidence of multifocal glioblastoma has been seen with carcinoma breast, indicating a possible role of the BRCA-1 gene in the pathogenesis.^[21] A two-hit hypothesis has also been suggested.^[6,21] The IDH mutation status did not seem to correlate with the multifocality in our series. However, two of our patients with Grade II insular astrocytoma had p53 mutation, while one glioblastoma patient (#5) was having wild p53, and the information was not available in Grade III astrocytoma patient (patient #1). Therefore, in this series, multifocality in insular glioma resulted from all grades of gliomas, being more common in aggressive tumor types (4/5, 80%, either a high-grade glioma or p53 mutation in Grade II astrocytoma). That said, we did not find any difference in p53 mutation status with respect to the unifocal tumors. However, exclusive involvement of the right insula and the male gender were the striking findings of our study. Moreover, the involvement of younger patients was also an interesting finding.

Pathologically, the tumors may be of the same or sometimes different histology.^[6,7] In our series, we found a

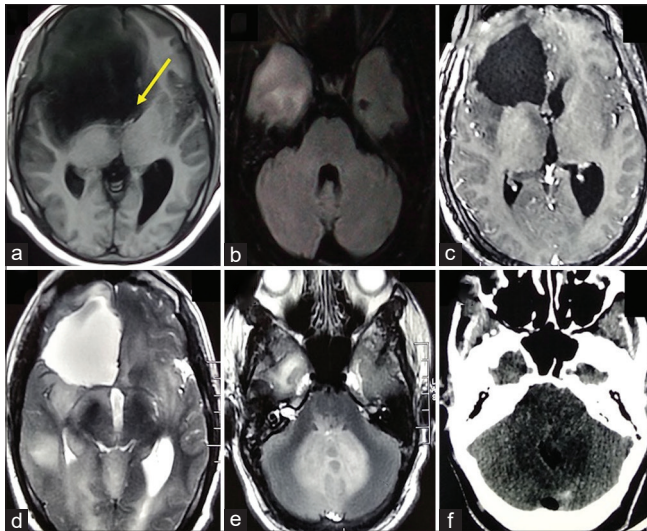


Figure 5: Preoperative magnetic resonance axial images (a and b) showing large right insular mass with patchy enhancement, Yasargil type 5B, and there was no lesion in the posterior fossa at that time. The lesion had an unusual basifrontal extension for insular glioma and extended into the ventricle (arrow). Postoperative magnetic resonance images (c and d) demonstrate a subtotal insular tumor excision with a residual tumor in the posterior insula. Magnetic resonance T2 axial (e) shows a single midline cerebellar mass after 2 years of follow-up, which was not present previously. The cerebellar lesion was subtotally resected, as shown in postoperative computed tomography (f)

histological similarity in two patients where the information was available. In low-grade gliomas, it has been stated that the secondary lesion almost always spreads from the primary site.^[22] In all except patient #5, the tumors could be interlinked via the ventricular cerebrospinal fluid (CSF) pathway. Insular gliomas often abut the temporal horn of the lateral ventricle, and theoretically, the tumor cells may be shed into the ventricles. Moreover, we saw that two patients (patients #2 and 3) had an intraventricular tumor extension. Therefore, it is clear that the part of the insular glioma touching/entering the ventricle or the subventricular zone enhances the risk of inherently aggressive tumor types (high grade or with an aggressive molecular profile).^[23] However, patient #1 had a relatively smaller, albeit enhancing insular tumor, and the postoperative histology suggested a diagnosis of anaplastic astrocytoma. Therefore, we can assume that the tumor margins in this patient proliferated at a higher rate and must have contacted the ventricle for an intraventricular spread. In patient #4, insular glioma resection was combined with an anteromedial temporal resection. Therefore, iatrogenic temporal horn entry and subsequent tumor dissemination appeared likely in this case. In patient #2, the multifocality appeared despite a Grade I tumor histology. There are reports of Grade I gliomas having leptomeningeal spread and presenting multifocally.^[24,25] Patient #5 was a case of glioblastoma, and it appeared at anatomically unconnected locations. The insula and the premotor area are preferred sites of low-grade glioma due to their cytoarchitectural, functional, and molecular characteristics.^[6] However, we are not aware

of any previous reports to suggest a similar predilection for high-grade gliomas. Since this was an old patient with IDH wild-type glioblastoma, it cannot be ascribed to secondary anaplastic transformation of low-grade glioma. Therefore, it represented a true multicentric tumor as per the definition. A case of bilateral insular glioma was reported explaining a similar multicentricity.^[5]

Apart from the CSF pathway, the Duffau group has shown that insular gliomas tend to spread through the subcortical association tracts.^[26-28]

Management issues

A diagnostic dilemma is often faced in the setting of multifocal gliomas, particularly in synchronous presentations. However, younger age and a typical pattern of spread were the points against cerebral metastasis in our series. Patient #5 was an old patient presenting with two enhancing lesions, a known linkage between the two could not be established. Hence, we considered a possibility of metastasis here, and a positron emission tomogram scan was performed preoperatively in this patient which ruled out any extracranial primary. Intracranial metastasis in the insula is extremely rare, and therefore, the diagnosis of metastasis in the brain was remote in any of our patients.

A stereotactic biopsy is generally recommended in multifocal tumors, and further decisions rely on the histopathology findings.^[6] If the histology is glioma, surgical excision is known to improve survival.^[6,28] On the other hand, a metastatic lesion undergoes surgery or radiosurgery depending on the histology, size, and tumor location.^[10,28] We had three patients (patients #1, 2, and 5) who presented with synchronous tumors in our series. The insular tumor was the cause of symptoms in all, and this area is not suitable for a stereotactic biopsy. Therefore, surgical excision of the insular glioma was conducted. We resected the second lesion in patient #5 due to the preoperative suspicion of a high-grade tumor or an occult primary. Therefore, if the two lesions are accessible during the same approach, it is preferable to remove both to improve the survival.

Barring the patient with insular DNET, the rest of the patients died within months of surgery. Therefore, insular multifocal glioma, like in any other site, is a fatal disease with poorer outcomes than unifocal tumors.^[2] The poor prognosis has been corroborated in many previous studies.

Conclusion

Insular glioma can rarely present with a multifocal disease or develop postoperative CSF dissemination. Interestingly, the condition was exclusively found in males and affected the right insula in all of them. A higher tumor grade or unfavorable mutation of the p53 gene appears to portend a higher risk; however, it is safe to say that many more intricate mechanisms probably underpin this condition.

CSF pathway dissemination could be established in 80% of the cases, either by the tumor itself or by iatrogenic ventricular dissemination. True multicentric insular glioma is extremely rare. The prognosis in the face of multifocality in non-Grade I gliomas is poor.

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Conflicts of interest

There are no conflicts of interest.

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