American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e923928
DOI: 10.12659/AJCR.923928

Received: 2020.03.01
Accepted: 2020.04.14
Available online: 2020.05.21
Published: 2020.05.28

Whole Exome Sequencing of Multiple Atypical Meningiomas in a Patient without History of Neurofibromatosis Type II: A Case Report

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Conflict of interest: None declared

Patient: Female, 39-year-old
Final Diagnosis: Atypical meningioma • meningioma • multiple meningioma
Symptoms: Headache
Medication: —
Clinical Procedure: Surgery and radiotherapy
Specialty: Neurosurgery

Objective: Unusual clinical course

Background: The pathogenesis of sporadic multiple meningiomas in the patients without history of neurofibromatosis type II remains unclear. We report whole exome sequencing (WES) of 2 metachronous multiple meningiomas of the same patient.

Case Report: A 39-year-old female had a 5-month history of headache and her magnetic resonance imaging (MRI) revealed a significantly enhanced intracranial space-occupying pathology with dura tail sign and skull invasion. She had no history of neurofibromatosis type II or other tumors. Tumor resection achieved Simpson grade I and the pathological studies revealed an atypical meningioma. After surgery, she accepted focal external-beam radiation therapy. One year later, MRI showed a significantly enhanced intracranial space-occupying pathology near the primary site of the previous tumor. She had only a mild headache. Simpson grade I resection of the tumor was achieved. The pathological diagnosis was still an atypical meningioma. WES on both tumors identified 220 common somatic gene mutations and 43 different somatic gene mutations. Three deleterious mutated genes including *QRICH2*, *KIF2C*, and *MUC16* were identified only in the first tumor, and 9 deleterious mutated genes including *FCGBP*, *RPS6KA5*, *GOLGA6L2*, *IGHV3-66*, *RPTN*, *AGRN*, *USP6*, *CLTCL1*, and *PABPC3* were identified only in the second tumor. As shown by the identical result of 3 prediction tools, *RPS6KA5* and *AGRN* were most likely to be related to the progress of multiple atypical meningiomas.

Conclusions: The metachronous meningiomas with same World Health Organization (WHO) grades in the same patient could have distinct genetic aberration patterns. The roles of *RPS6KA5* and *AGRN* in the rapid progress of multiple atypical meningiomas need further studies.

MeSH Keywords: Exome • Meningioma • Neoplasm Recurrence, Local

Abbreviations: **CSF** – cerebrospinal fluid; **MRI** – magnetic resonance imaging; **WES** – whole-exome sequencing; **RPS6KA5** – ribosomal protein S6 kinase A5; **ERK/MAPK** – extracellular-regulated kinase/mitogen-activated protein kinase

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/923928

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Background

Multiple meningiomas are defined as the presence of ≥2 independently situated synchronous or metachronous meningiomas, which occur in <10% of patients with meningioma, whether or not the tumors have the same pathologic subtypes [1–3]. The pathogenesis of solitary meningiomas has been studied, but multiple meningiomas have their own clinical features. The pathogenesis of multiple meningiomas has not been well known. It can occur sporadically or as part of a familial syndrome of either neurofibromatosis type II or familial multiple meningiomas [4]. The incidence of sporadic multiple meningiomas without history of neurofibromatosis type II was low [5]. Multiple meningiomas usually show a uniform histology, but the synchronous meningiomas of different grades have been reported and may be formed independently due to separate genetic mutation and aberrant pathway expressions [6]. Most of the published series considered multiple meningiomas as a class that was histologically benign [3]. The multiple atypical meningiomas are not common. There have been 7 previous reports on the cases of synchronous multiple meningiomas, 2 of which included whole exome sequencing (WES) [6]. But there has seldom been a study on cases with metachronous multiple meningiomas. To clarify the difference in molecular biology between the nodules may be useful to explore the genetic events underlying the pathogenesis of multiple meningiomas. We report a case with metachronous multiple meningiomas and the difference between the WES of 2 nodules.

Case Report

The patient was a 39-year-old female who had a 5-month history of intermittent headache. Magnetic resonance imaging (MRI) revealed a significantly enhanced intracranial space-occupying pathology with dura tail sign and skull invasion (Figure 1). She had no history of neurofibromatosis type II or other tumors. She was diagnosed with meningioma. Before the operation, a titanium plate was prepared with 3-dimensional (3D) printing technology based on the skull invasion area. A craniotomy was carried out under general anesthesia. The tumor has penetrated the dura mater and the skull and destroyed the periosteum and the galea. The surface of brain has been invaded by the tumor and softened. The dura mater near the base of tumor was thickened, which was consistent with the dura tail sign area on MRI. The destroyed skull was honeycombed. The tumor, the abnormally thickened dura mater, the abnormal skull and the destroyed galea were removed. A few thickened dura mater approaching the midline was designedly remained. Tumor resection achieved Simpson grade I (Figure 2). The dura mater and the skull were repaired with artificial dura mater and titanium plate. She had an uneventful post-operative course. The pathological studies revealed an atypical meningioma with Ki-67 index of 40% and positive p53 expression. After surgery, she accepted external-beam radiation therapy. She was followed up with contrast-enhanced MRI once every 3 months and there was no recurrence. However, 1 year later, the fourth MRI follow-up showed a significantly enhanced intracranial space-occupying pathology a short distance nearby the primary site of the previous tumor (Figure 3). She had only a mild headache. She was re-operated and achieved Simpson grade I resection of the tumor. As found during the surgical procedure, the base of the new tumor was located in the temporal side and a short distance to the margin of the field of the last operation. Her postoperative recovery was smooth. The pathological diagnosis was still an atypical meningioma with Ki-67 index of 40% and positive p53 expression.

After evaluating the detailed pathology history, availability of tissue specimens, and availability of high-quality DNAs, the specimens of these 2 meningiomas were collected to WES

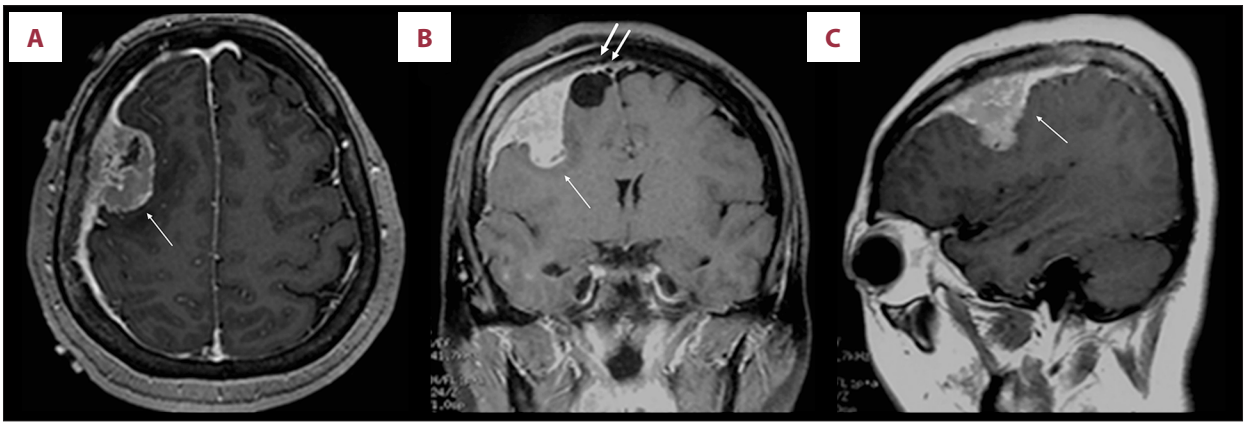

Figure 1. The contrast-enhanced magnetic resonance images of the primary atypical meningioma. (**A**) The axial view; (**B**) the coronal view; (**C**) the sagittal view. Single arrow: the interface between the meningioma and the brain. Double arrows: the dura tail sign area near the midline.

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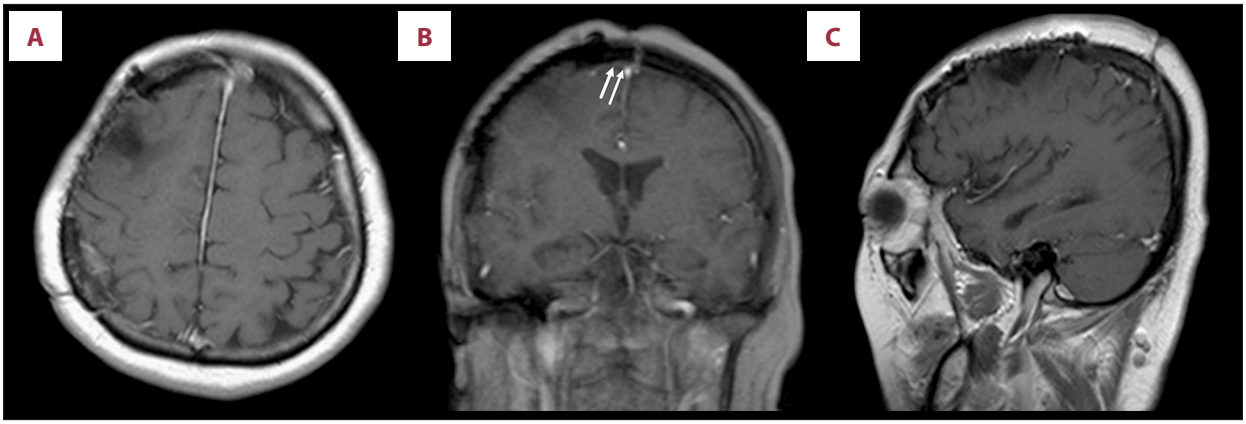

Figure 2. The eighth-month follow-up of the contrast-enhanced magnetic resonance images after surgery. (**A**) The axial view; (**B**) The coronal view; (**C**) the sagittal view. Double arrows: the dura tail sign area near the midline.

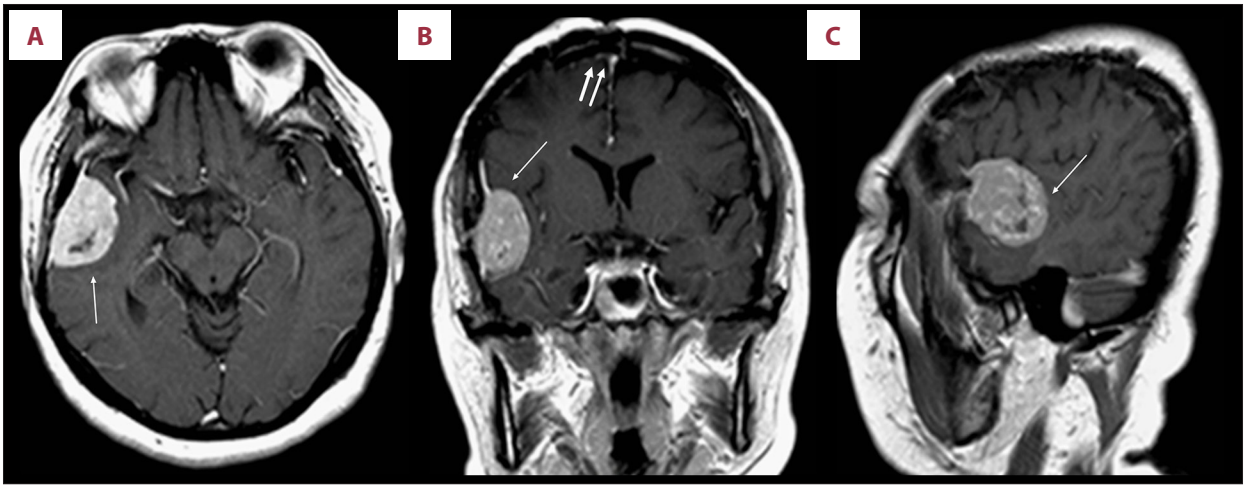

Figure 3. The twelfth-month follow-up contrast-enhanced magnetic resonance images showed the second atypical meningioma. (**A**) The axial view; (**B**) the coronal view; (**C**) the sagittal view. Single arrow: the interface between the meningioma and the brain. Double arrows: the dura tail sign area near the midline.

and germline DNA extraction, which was performed by Beijing Genetron Health Biotechnology Co., Ltd.

As shown in Table 1, the data analysis identified 220 common somatic gene mutations including 42 deleterious somatic gene mutations, and 43 different somatic gene mutations including 12 deleterious somatic gene mutations. Three deleterious mutated genes including *QRICH2*, *KIF2C*, and *MUC16* were identified only in the first atypical meningioma, and 9 deleterious mutated genes including *FCGBP*, *RPS6KA5*, *GOLGA6L2*, *IGHV3-66*, *RPTN*, *AGRN*, *USP6*, *CLTCL1*, and *PABPC3* were identified only in the second atypical meningioma. As shown by the identical result of 3 prediction tools, among these mutations, *RPS6KA5* and *AGRN* were most likely to be related to the progress of multiple atypical meningiomas.

Discussion

The studies on the metachronous multiple meningiomas have been scarce. For patients with multiple meningiomas whose new tumors appeared after early tumor resection or radiation therapy, it is sometimes difficult to distinguish the new tumor of multiple meningiomas from the recurrence or radiation-induced tumor. Just as in the present case, it is a question to consider; is the second tumor recurrence or radiation-induced one? Radiation-induced meningiomas are located exclusively at the site of x-ray exposure [2]. The second tumor of the present case was not radiation-induced because it was located outside the target field of previous radiation. It has been suggested that the patients with 1 or more than 1 tumor in a regional or distant site after resection of a malignant meningioma should not be included in cases of multiple meningiomas because their tumor cells could spread or metastasize along the cerebrospinal fluid (CSF) despite radical

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Table 1. Overview of somatic DNA variants found in the different nodules.

Gene name	Variant classification	Chromosome	Tumor mutant frequency	Mutation assessor	SIFT	Polyphen2	cDNA change	Protein change
Unique variants in the first tumor								
QRICH2	Missense variant	17	0.35	T; 0.38878; 0.1057	Deleterious (0.02)	Possibly damaging (0.485)	c.1900G>A	p.Gly634Ser
KIF2C	Missense variant	1	0.17647	T; 0.10035; 0.0246	Deleterious (0)	benign (0.027)	c.1448G>T	p.Arg483Ile
MUC16	Missense variant	19	0.1037	T; 0.41166; 0.1147	.	Probably damaging (0.946)	c.40672A>C	p.Lys13558Gln
Unique variants in the second tumor								
FCGBP	Missense variant	19	0.48571	T; 0.70824; 0.3268	Deleterious (0.03)	Probably damaging (0.999)	c.4033G>A	p.Gly1345Ser
RPS6KA5	**Missense variant**	**14**	**0.39713**	**D; 0.88310; 0.6402**	**Deleterious (0)**	**Probably damaging (0.999)**	**c.1768G>A**	**p.Ala590Thr**
GOLGA6L2	Missense variant	15	0.23529	.; .; .	Deleterious low confidence (0)	Unknown (0)	c.1975G>A	p.Glu659Lys
IGHV3-66	Missense variant	14	0.20455	.; .; .	Deleterious low confidence (0.05)	Possibly damaging (0.451)	c.292T>C	p.Tyr98His
RPTN	Missense variant	1	0.17256	T; 0.04861; 0.0131	Deleterious (0)	Benign (0.276)	c.460A>G	p.Arg154Gly
AGRN	**Missense variant**	**1**	**0.12281**	**D; 0.89829; 0.6828**	**Deleterious (0.02)**	**Probably damaging (0.993)**	**c.5501C>T**	**p.Pro1834Leu**
USP6	Missense variant	17	0.10127	T; 0.12987; 0.0315	Deleterious low confidence (0)	Benign (0.005)	c.240G>T	p.Met80Ile
CLTCL1	Missense variant	22	0.09877	T; 0.24353; 0.0590	Deleterious (0)	Possibly damaging (0.893)	c.3493C>T	p.Arg1165Cys
PABPC3	Missense variant	13	0.06716	T; 0.49490; 0.1560	Deleterious (0.03)	Benign (0.185)	c.1799C>A	p.Ser600Tyr

excision [3]. However, the second tumor of the present case appeared distal from the primary site of the first tumor and at least 8 months after surgery and grew rapidly within a short time period, while the residual abnormal thickened dura mater that was the dura tail sign of the first tumor did not develop on MRI follow-up. Thus, although both tumors were atypical meningiomas, the present case should be diagnosed as multiple meningiomas.

The molecular mechanisms underlying the pathogenesis of sporadic multiple meningiomas have not yet been clarified. Two hypotheses have been proposed in the literature [2,7]. One is that most multiple meningiomas are of monoclonal in origin, the other is that multiple meningiomas originate from multiple foci and are not the result of cell migration along CSF. Our data identified 220 common somatic gene mutations including 42 deleterious somatic gene mutations, and 43 different

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somatic gene mutations including 12 deleterious somatic gene mutations. It showed the overlapping but distinct genetic aberration features underlying them, which supported their monoclonal origins in the same patient followed by independent mutations [3].

The advent of WES made it possible to identify candidate genes and pathways from a large body of information about the mutational landscape of meningiomas. The WES studies have revealed that the most common alterations in the sporadic meningiomas are *NF2* mutations or loss of 22q, but the remaining non-NF2 mutant meningiomas harbor some new driver mutations including *TRAF7, KLF4, AKT1, SMO, PIK3CA, NOTCH2, SMARCB1, CHEK2, SMARCE1*, *DAL1* (*EPB41L3*), *TP73*, *hRAD54*, and *POLR2* [8–10]. To our knowledge, our study was the first to compare the WES of the nodules of multiple atypical meningiomas.

Our data identified 3 unique deleterious mutated genes in the first atypical tumor and 9 unique deleterious mutated genes in the second atypical tumor. As shown by the identical result of 3 prediction tools, *RPS6KA5* and *AGRN* were most likely to be related to the rapid development of the second tumor which was an atypical meningioma. The present study lacked blood WES analysis, which made it difficult to distinguish somatic mutations from germline mutations. However, it did not affect the result because the samples of the 2 tumors were from the same patient.

RPS6KA5, also described as *MSK1*, *MSPK1*, or *RLPK*, is a member of *P90*^{RSK} family. It is widely expressed in many tissues of human beings. It is responsible for the regulation of ribosomal S6 protein activity. It has been shown to be involved in the *ERK/MAPK* signaling pathway. It encodes *MSK1*, which is a mitogen- and stress-activated protein kinase and is activated by *ERK* and *p38 MAPK* in response to growth factors and cellular stress [11]. *MSK1* mediates histone*H3* phosphorylation and immediate-early gene expression and transmits external signals into various responses involved in cancer development [12]. The MAPK signaling pathway is one of the most important regulatory pathways, and its signal-related proteins are widely distributed in the nucleus, cytoplasm, mitochondria, and Golgi participating in regulating the various life activities of the body. It has been proven that the *ERK/MAPK* signaling pathway could regulate cell proliferation and invasion and promote the development and metastasis of colorectal cancer. Our data revealed the first meningioma to express *RPS6KA5* mutation, and the correlation between the *ERK/MAPK* signaling pathway and the development of atypical meningioma or multiple meningiomas has never been reported. The role of *RPS6KA5* and the *ERK/MAPK* signaling pathway in the pathogenesis of atypical meningioma or multiple meningioma should be further studied.

WES revealed a missense variant in the *AGRN* gene, which encodes agrin. Agrin is a heparin sulfate proteoglycan. It has been reported that *AGRN* was involved in the proliferation, migration, and invasion of liver cancer cells by regulating focal adhesion integrity [13]. The loss of *AGRN* has also been described in human glioblastoma [14]. The correlation between *AGRN* and meningioma has never been described. Our data revealed the first case with meningioma which expressed *AGRN*. The role of *AGRN* in development of multiple meningioma or atypical meningioma is worth further study.

Although meningioma is the most common primary tumor of the central nervous system, the mechanism of progression from benign to atypical or anaplastic grade remains elusive [5]. It has been suggested that the atypical tumor may have progressed from the benign tumor. Our case proved that the meningiomas could be atypical or anaplastic from the beginning. The roles of *RPS6KA5* and *AGRN* in the pathogenesis of atypical meningiomas are worthy of study. To the best of our knowledge, this is the first study to adopt WES to compare the genetic profiling of 2 metachronous atypical meningiomas in the same patient with sporadic multiple meningiomas.

Conclusions

Metachronous meningiomas with the same World Health Organization (WHO) grades in the same patient could have distinct genetic aberration patterns. The roles of *RPS6KA5* and *AGRN* in the rapid progress of multiple atypical meningiomas need further studies.

Acknowledgements

We thank Dr. Feilong Zhao (Division of Medicine and Research, Genetron Health (Beijing) Co. Ltd., Beijing, China) for assistance with data analysis.

Conflict of interests

None.

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