Fluorescent In Situ Hybridization 1p/19q Deletion/Imbalance Analysis of Low-Grade and Atypical Meningiomas

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Abstract

The chromosomal 1p/19q state was analyzed in 16 low-grade meningiomas and 7 atypical meningiomas using fluorescent in situ hybridization (FISH) analysis. Chromosome 1p aberrations were observed in all atypical meningiomas, but in only one low-grade meningioma. Atypical meningiomas showed 19q deletion or imbalance, suggesting chromosomal instability of 19q. A small group of low-grade meningioma showed 19q aberrations. FISH 1p/19q deletion/imbalance analysis is a sensitive method for detecting chromosome aberrations of meningiomas and provides useful information for grading of meningiomas. Patients with low-grade meningioma with chromosomal instability of 1p/19q should be followed up carefully. Assessment of the chromosomal state by FISH might be of crucial importance in the clinical management of meningiomas.

Key words: meningioma, fluorescent in situ hybridization, chromosome 1p/19q, chromosomal instability

Introduction

Meningiomas are common intracranial tumors arising from arachnoidal cells. Most meningiomas are benign (World Health Organization [WHO] grade I), but atypical meningiomas (WHO grade II) constitute between 4.7% and 7.2% of meningiomas, and anaplastic meningiomas (WHO grade III) account for 1.0–2.8%.¹¹⁾ Both atypical and anaplastic meningiomas demonstrate histological and clinical features suggesting aggressive potential, and show a tendency for tumor recurrence, even after complete resection. Histological findings, such as increased cellularity, uninterrupted patternless growth, and mitotic figures may be helpful, but these subtle differences may not be readily apparent on routine hematoxylin-eosin staining, and may require measurement of MIB-1 labeling index to assess the proliferative activity. High MIB-1 labeling index is considered to be closely correlated with the histolog-

ical grading of malignancy. The WHO classification of atypical meningioma requires increased mitotic activity of 4 or more mitoses per 10 high-power fields.¹⁰⁾ However, the correct cutoff value for these continuous variables is difficult to establish. Histological grades and MIB-1 labeling index have a fairly good correlation, but MIB-1 labeling index shows significant overlap between benign, atypical, and anaplastic meningiomas.¹¹⁾ Therefore, these diagnostic markers of proliferation have limitations, and there is a need for a more precise, efficacious, and objective approach to the diagnosis and grading of meningiomas. Genetic characterization is another possible alternative for grading of meningiomas.^{2,16,18–20)}

The present study explored the potential diagnostic utility of genetic alterations by comparing the histological features and chromosomal states in a series of meningiomas using fluorescent in situ hybridization (FISH).

Table 1 Cases of low-grade and atypical meningiomas

Case No.	Age (yrs)/ Sex	Location	Subtype	WHO grade	MIB-1 LI (%)	FISH diagnosis		1p Normal (%)	1p Abnormality (total, %)	19q Normal (%)	19q Abnormality (total, %)
						FISH 1p	FISH 19q				
1	42/M	olfactory groove	trans	I	0.2	normal	normal	96.2	3.8	92.6	7.4
2	62/M	jugular foramen	men	I	1.5	normal	normal	97.3	2.7	97.7	2.3
3	69/F	suprasellar	men	I	0.6	normal	normal	90.1	9.9	92.6	7.4
4	71/F	parasagittal	trans	I	0.8	normal	mono.	89.9	10.1	44.5	55.5
5	69/F	convexity	fibrous	I	0.1	normal	normal	92.1	7.9	90.0	10.0
6	72/F	convexity	angio	I	0.1	normal	normal	98.5	1.5	92.0	8.0
7	70/F	parasagittal	fibrous	I	0.4	normal	normal	94.5	5.5	95.5	4.5
8	75/M	falx	angio	I	0.7	normal	poly.	75.5	24.5	55.0	45.0
9	80/F	tuberculum sellae	men	I	1.2	normal	normal	96.5	3.5	99.0	1.0
10	70/M	tentorium	men	I	2.5	normal	normal	94.5	5.5	99.0	1.0
11	44/M	parasagittal	men	I	1.0	normal	normal	96.0	4.0	95.5	5.0
12	54/F	petroclival	men	I	0.8	normal	normal	92.6	7.4	94.4	5.6
13	41/M	convexity	men	I	2.0	normal	normal	100.0	0	96.0	4.0
14	45/F	parasagittal	fibrous	I	0.4	normal	normal	94.7	5.3	85.0	15.0
15	64/F	convexity	metapla	I	0	normal	normal	87.0	13.0	99.0	1.0
16	22/F	convexity	trans	I	7.8	def. deletion	normal	15.0	85.0	95.0	5.0
17	56/F	tentorium	atyp	II	8.2	dispro. deletion	amp.	3.6	96.4	9.4	90.6
18	48/F	ventricle	atyp	II	5.0	deletion with imb.	amp.	8.5	91.5	8.7	91.3
19	62/F	convexity	atyp	II	3.5	dispro. deletion	normal	7.8	92.2	63.8	36.2
20	78/M	convexity	atyp	II	6.3	def. deletion	def. deletion	15.0	84.5	16.7	83.3
21	79/F	convexity	atyp	II	3.5	def. deletion	imb.	17.3	82.7	44.2	55.8
22	55/F	tentorium	atyp	II	1.5	def. deletion	normal	14.0	86.0	63.0	37.0
23	60/F	sphenoid ridge	atyp	II	1.2	def. deletion	normal	24.1	75.9	57.5	42.5

Contd.

Materials and Methods

Tumor samples were collected from 16 consecutive surgically resected low-grade meningiomas, and 7 consecutive atypical meningiomas including 3 archival and 4 fresh samples obtained from 23 patients, 16 females and 7 males aged 22–80 years (mean 60.3 years). The locations of the tumors are shown in Table 1. All tumors were classified by histological examination and graded according to WHO guidelines.¹⁰⁾ The diagnostic criteria for atypical meningioma were based on increased mitotic activity defined as 4 or more mitoses per 10 high-power fields or 3 or more of increased cellularity, small cell with high nucleus/cytoplasm ratio, prominent nucleoli, uninterrupted patternless or sheet-like growth, and necrotic foci.¹⁰⁾

FISH analysis used a touch preparation of fresh

samples. The material was prepared with Carnoy's fixation and denatured at 80°C for 5 minutes. Cell copy numbers were investigated by FISH using Vysis® LSI 1p36/1q25 and LSI 19q13/19p13 Dual-Color Probe (Abbott Laboratories, Abbott Park, Ill., U.S.A.). Signals were counted for each hybridization in randomly chosen regions of at least 200 nonoverlapping nuclei with intact morphology. Parallel touch preparation methods, prepared from the same surface as the hybridized slide, were used to confirm the successful collection of tumor cells. Parallel touch preparations for each tumor was stained with Papanicolaou stain and reviewed by a cytopathologist to identify the fraction of tumor cells. Tissues from archival samples were prepared as described before.¹²⁾

Assessment and interpretation of FISH results used the previously published criteria modified for

Table 1, contd.

Subtype of 1p abnormality (%)								Subtype of 19q abnormality (%)							
Mono.	Poly.	Instability except for mono. and poly.						Mono.	Poly.	Instability except for mono. and poly.					
		Def. deletion	Dispro. deletion	Imb.	Amp.	Other aberration	Total			Def. deletion	Dispro. deletion	Imb.	Amp.	Other aberration	Total
0	0	1.9	0	0	1.9	0	3.8	0.6	2.5	2.8	0	0	1.9	0	4.7
0	2.7	0	0	0	0	0	0	0	2.3	0	0	0	0	0	0
0	0.9	9.0	0	0	0	0	9.0	0.5	0.9	6.0	0	0	0	0	6.0
0	1.6	3.2	0	1.1	4.2	0	8.5	<u>48.9</u>	0	1.8	0	0	4.8	0	6.6
0.4	4.8	0.4	0	1.5	0.8	0	2.7	<u>0.9</u>	4.4	0.9	0	0	3.8	0	4.7
0.5	0	0.5	0	0	0.5	0	1.0	0	7.5	0.5	0	0	0	0	0.5
0	5.5	0	0	0	0	0	0	0.5	3.5	0	0	0.5	0	0	0.5
3.0	12.5	8.5	0	0.5	0	0	9.0	1.5	<u>37.5</u>	0.5	0	2.5	3.0	0	6.0
0	3.5	0	0	0	0	0	0	0	1.0	0	0	0	0	0	0
0	0.5	5.0	0	0	0	0	5.0	0	0.5	0.5	0	0	0	0	0.5
0	4.0	0	0	0	0	0	0	0	5.0	0	0	0	0	0	0
0	6.5	0.9	0	0	0	0	0.9	0	3.7	1.9	0	0	0	0	0
0	0	0	0	0	0	0	0	0	4.0	0	0	0	0	0	0
0	5.3	0	0	0	0	0	0	2.4	10.8	0	1.8	0	0	0	1.8
5.0	7.0	1.0	0	0	0	0	1.0	0	0	1.0	0	0	0	0	1.0
0	0	<u>83.0</u>	0.0	2.0	0	0	85.0	0	2.0	1.0	0	2.0	0	0	3.0
6.8	0	<u>37.4</u>	<u>44.2</u>	4.9	0.4	2.7	89.6	10.8	1.0	1.5	0	0	<u>74.8</u>	2.5	78.8
2.3	3.8	<u>23.0</u>	<u>32.0</u>	<u>27.2</u>	3.2	0	85.4	1.3	5.7	0.9	0	0.9	<u>82.7</u>	0	84.5
9.1	1.4	<u>28.7</u>	<u>44.8</u>	4.8	1.7	1.7	81.7	9.5	1.0	9.0	1.4	0.5	14.8	0	25.7
0	0	<u>84.5</u>	0	0	0	0	84.5	0	0.3	<u>82.1</u>	0	0	0.9	0	83.0
0.6	0.6	<u>76.3</u>	0	5.2	0	0	81.5	0	0	3.4	0	<u>52.4</u>	0	0	55.8
11.0	0	<u>60.0</u>	0	15.0	0	0	75.0	2.0	19.0	4.0	0.0	4.0	8.0	0	14.0
0.9	0	<u>73.1</u>	0	1.9	0	0	75.0	0	16.4	15.7	0.7	1.5	8.2	0	26.1

Abnormalities exceeding 20% are underlined. angio: angiomatous meningioma, amp: amplification, atyp: atypical meningioma, def.: definitive, dispro.: disproportional, fibrous: fibrous meningioma, FISH: fluorescent in situ hybridization, imb.: imbalance, LI: labeling index, men: meningothelial meningioma, metapla: metaplastic meningioma, mono.: monosomy, poly.: polysomy, trans: transitional meningioma, WHO: World Health Organization.

brain tumors (Table 2).¹²⁾ Deletion or imbalance was defined as alterations detected in >20% of the nuclei. Comparison of intact nuclei from fresh cell preparations and truncated nuclei in paraffin sections showed that nuclear truncation resulted in approximately 5–9% signal loss.^{1,4)} Nuclear truncation due to sectioning or other artifacts in the hybridization process could increase the false-positive signal deletion. Therefore, we adopted a cut-off value of 20% for FISH analysis.¹²⁾

All tumors were evaluated for the expression of proliferation-associated nuclear antigen Ki-67 (MIB-1) using formalin-fixed paraffin sections. Images captured with a digital camera were analyzed quantitatively with a free software package, Scion

Image (Scion Corporation, Frederick, Md., U.S.A.), to count the number of cells labeled with MIB-1. All results were reviewed by manual measurements to confirm this computer-assisted technique.

The relationships between 1p/19q deletion or imbalance and histological grade were analyzed using the Fisher exact test. P values of <0.05 were considered statistically significant. All samples were tested according to an institutional review board-approved protocol.

Results

The diagnoses and histological subtypes of the tumors are shown in Table 1. Table 1 also summa-

Table 2 Definitions of chromosome status by fluorescence in situ hybridization (FISH)

FISH—Chromosome 1p36	
Deletion:	one or less signal for chromosome 1p36 (ratio 0/1, 0/2, 1/2, 1/3, 1/4 etc.)
Definitive deletion:	one or less signal for chromosome 1p36 in relation to normal reference probe signals on chromosome 1q25 (ratio 1/2, 0/2)
Disproportional deletion:	one or less signal for chromosome 1p36 with disproportion of the ratio of the reference probe (ratio 1/3, 1/4 etc.)
Deletion with reference deletion:	chromosome 1p36 deletion with deletion of reference region (ratio 0/1)
Imbalance:	imbalance of the ratio of the reference probe to chromosome 1p36 with more than two reference probe signals (ratio 2/3, 3/4, 3/5 etc.)
Polysomy:	simultaneous increase of both signals (ratio 3/3, 4/4, 5/5 etc.)
Monosomy:	simultaneous decrease of both signals (ratio 1/1)
Amplification:	target signal > reference signal per cell (ratio 3/2 etc.)
Normal:	no deletion, no imbalance and no polysomy detected by FISH with the probes used (ratio 2/2)

Fig. 1 A, B: Photomicrographs of samples of atypical meningioma showing uninterrupted patternless growth with mitotic figures (A: hematoxylin and eosin stain, original magnification $\times 400$), and MIB-1 labeling showing active proliferation (B: immunohistochemistry for Ki-67, original magnification $\times 400$). C, D: Fluorescent in situ hybridization analysis of chromosomal arms 1p/19q showing 1p36 deletion status with a 2:1 ratio of control (green) signals and target (red) signals (C), and 19q13 imbalance status with 3:2 and 5:2 ratios of control (green) signals and target (red) signals (D).

rizes the genomic abnormalities of 1p/19q status detected by FISH (Fig. 1) in the 23 tumors studied. The mean MIB-1 labeling index was not significantly higher for atypical meningiomas (mean 4.2%) than

for low-grade meningiomas (mean 1.3%). All 7 atypical meningiomas showed chromosome 1p deletion including disproportional deletion and imbalance, and the cell population with 1p deletion accounted for over 50% of the tumor in all cases. In contrast, 1p deletion was detected in only one of the 16 low-grade meningiomas. Six of the 7 atypical meningiomas had 19q instability including deletion, imbalance, or amplification, whereas 2 of 16 low-grade meningiomas demonstrated 19q monosomy or polysomy (Table 1). These FISH analyses showed the genomic abnormalities of 1p/19q status of atypical meningiomas were significantly different from those of low-grade meningioma ($p < 0.05$ for both locations).

Discussion

FISH is a powerful tool for the assessment of target deoxyribonucleic acid dosages in interphase nuclei without paired blood samples and has been used for evaluating numerical and structural genomic aberrations in various tumors.^{5,12,13,17} The primary advantages are applicability to archival, formalin-fixed paraffin-embedded material and morphological preservation, which is particularly attractive for studies on heterogeneous tissue samples without the need for microdissection. Detectable genomic alterations include deletion, imbalance, polysomy, translocation, and gene amplification. However, consensus criteria for assessment and interpretation of analytical results in brain tumors have not been established.¹² The present study used the criteria modified for brain tumors (Table 2). According to these criteria, “deletion” is defined as only one or less target signal (1/2, 1/3, 1/4 etc.) and subdivided into “definitive” deletion (1/2, 0/2), “disproportional” deletion (1/3, 1/4 etc.), and deletion “with reference deletion” (0/1). “Imbalance” is defined as disproportion of the signal ratio (2/3, 3/4, 3/5 etc.). FISH is a sensitive method for evaluating numerical genomic abnormalities at the cytogenetic level. It is also important to distinguish “disproportional” deletion and imbalance from “definitive” deletion among these chromosomal instabilities.

The present study used FISH with chromosome-specific probes to evaluate 1p and 19q chromosome aberrations in low-grade and atypical meningiomas. Our results showed genomic abnormalities in the 1p/19q status of atypical meningiomas, which were significantly different from the absence of abnormalities in low-grade meningioma. A few low-grade meningiomas showed abnormality of 1p/19q. Genetic changes associated with chromosome instability on chromosome 1p are important in both tumorigen-

esis and tumor progression in meningiomas. Frequency of loss of heterozygosity (LOH) on chromosome 1p tends to increase with tumor grade, as LOH on 1p was observed in 40% of grade 2 meningiomas and 70% of grade 3 meningiomas.¹⁶⁾ Chromosome 22q deletion and/or mutation of neurofibromatosis type 2 gene (NF2) are most frequently detected as the earliest genetic aberrations and found in meningiomas of all malignancy grades, indicating that inactivation of this gene represents an early event in the pathogenesis of meningiomas.^{14,15,19,20)} LOH for loci on chromosome 22q and mutations in the NF2 locus probably do not play a role in the development of malignancy in meningiomas.¹⁶⁾ Thus, the assessment of chromosome 22q is not suitable for the alterations associated with progression of meningiomas. LOH associated with meningioma progression has been extensively researched,^{2,16,18)} but only limited data on chromosomal aberrations by FISH are available.^{3,6,13-15)}

FISH analysis should be assessed as numerical genomic abnormalities at the cytogenetic level, not as the rate of chromosome gain or loss.^{6,14,15)} Assessment of FISH deletion status is useful for the evaluation of chromosomal instability of meningiomas. The frequency of deletions is proportional to histological grade and chromosome 1p deletion was identified in 23% of low-grade and 56% of atypical meningiomas.³⁾ Deletion of 1p occurred in 23–35% of low-grade meningiomas, and in 56–92% of the atypical meningiomas.^{3,13)} However, these previous FISH studies did not discriminate between deletion and imbalance status.

The present study showed that FISH 1p/19q deletion/imbalance analysis is a sensitive method for detecting chromosome aberrations of meningiomas and provides useful information for the grading of meningiomas. Specific details relative to FISH deletion status were not provided in all previous reports, so the frequency of specific deletion types cannot be compared with the present results. However, our results indicate that the frequency of 1p deletion in low-grade meningiomas may be lower than previously reported and further investigation is needed. The present study also demonstrated that atypical meningiomas have chromosomal instability of 19q including deletion, imbalance, and amplification.

Previous FISH studies analyzing 1p status in brain tumors have not compared MIB-1 labeling index and the chromosomal state.^{3,6,13-15)} The present results showed that MIB-1 labeling index is useful for grading meningiomas, but there is significant overlap. In contrast, FISH analysis of the 1p/19q status clearly distinguished atypical meningioma from low-grade meningioma. The diagnosis of meningio-

ma grade may depend on both assessment of proliferative state using MIB-1 labeling index and chromosomal state using FISH in the future.

In general, genetic changes precede morphological changes. Our results showed that a small group of low-grade meningiomas have 1p/19q aberrations. Whether such chromosome instability is an indicator of biological aggressiveness in histologically benign subgroups of meningiomas is extremely interesting. Some authors reported that meningiomas with chromosome 1p loss show the higher rate of recurrence occurring independently from the histological classification.⁷⁻⁹⁾ In our series, some low-grade meningiomas had FISH 1p definitive deletion and 19q monosomy or polysomy. Further investigation is needed to determine whether these low-grade meningiomas with chromosomal abnormality have high rates of recurrence and progression. Characterization of those genetic aberrations might facilitate the early identification of tumors with high intrinsic risk of progression. We plan to follow up patients with histologically benign meningiomas with a high percentage of 1p/19q deletions or imbalance.

FISH 1p/19q deletion/imbalance analysis is a sensitive method for detecting chromosome aberrations in meningiomas and provides useful information for the grading of meningiomas. Assessment of both chromosomal state by FISH and proliferative state by MIB-1 labeling index might be important in the clinical management of meningiomas.

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Commentary

Meningiomas are the second most common primary tumor of the central nervous system. Atypical (grade II) and anaplastic/malignant (grade III) meningiomas, which are associated with a higher rate of recurrence and aggressive growth, account for about 10% of all meningiomas. To find certain sensible and reliable indicators for grading of meningioma is crucial and valuable. The genetic aspects of meningiomas have been studied intensively during the past decade. Chromosome 22q, 1p, 9q, 14q and 10q aberration have been detected to correlate with meningioma progression. In the present article, the authors conclude that FISH 1p/19q deletion/imbalance analysis is a sensitive method for detecting chromosome aberrations of meningiomas and provides useful information for the grading of meningioma. Chromosome 1p/19q loss of heterozygosity has been regarded as a molecular genetic characteristic for oligodendroglioma. Can 1p/19q deletion/imbalance be an indicator for meningioma grading, treatment choice and prognosis expectation? The authors have made a valuable contribution. To answer this question finally, more larger studies are expected in the future and the 1p/19q status in anaplastic meningioma needs further investigation.

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