MENINGIOMAS, the most common type of primary brain tumors in adults, comprise 26.4%–33.4% of all CNS tumors\(^3,4\) and are usually slow growing, benign, and rarely cause CSF dissemination. Atypical meningiomas, a subtype of meningiomas with increased mitotic activity or specific malignant histopathological features, comprise 4.7%–7.2% of all meningiomas and are classified as WHO Grade II.\(^10\) Including WHO Grade II and III meningiomas, only 38 cases of CSF dissemination have been reported. We describe 2 cases of atypical meningioma with ON seeding in patients who presented with subacute visual loss. This is the first report of meningiomas with CSF dissemination to the ON. The authors present the genetic characteristics of these atypical meningiomas with CSF dissemination. The patient in Case 1 was a 36-year-old woman with a 1.5-cm mass within the left ON, and the patient in Case 2 was a 70-year-old woman with a 0.9-cm mass around the right ON. Both individuals had undergone multiple surgeries for primary lesions and local recurrent lesions. They presented with subacute visual loss, and both tumors were completely resected. The pathological diagnosis was atypical meningioma with high MIB-1 indices and p53-positive cell ratios in each case. Comparative genomic hybridization showed significant chromosomal copy number alterations similar to the results of previous surgeries, confirming that the tumors were disseminated lesions. The present findings suggest that genetic characteristics, such as 1p and 10qcen-23 losses and 17q and 20 gains, shared by the 2 cases might be associated with CSF dissemination of meningiomas.

**Case Reports**

**Case 1**

**History.** This 36-year-old woman visited our hospital with rapidly worsening visual acuity. She had undergone two total resections for a 6-cm tumor in the left trigone, one 4 years previously and the other (for a local recurrence) 8 months previously (Fig. 1A and B). Conventional and stereotactic irradiation was performed. The pathological diagnosis was atypical meningioma because 5 mitoses were observed in 10 hpf. The MIB-1 index and p53-positive cell ratio were 10.0% and 8.4%, respectively. Copy number alterations detected by CGH included 1p, 3p24-ter, 10qcen-23, 16p, 18q, 22q, Xp, and Xq23-ter losses and 3pcen-21, 10q25-ter, and 17q gains (Fig. 2G). Subsequently, the patient, who was symptom free, was followed up as an outpatient.

Abbreviations used in this paper: CGH = comparative genomic hybridization; CNA = copy number alteration; ON = optic nerve.
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**Examination.** Examination of the patient’s left eye demonstrated no light perception, and her right visual acuity was 20/200 with an extremely narrow visual field (Fig. 1C). Brain MRI revealed a 1.5-cm mass around the left ON and optic chiasm (Fig. 1D and E). Emergency surgery via a left frontotemporal approach revealed that the tumor developed within the left side of the optic chiasm and deeply invaded the ON, without dura mater attachment (Fig. 2A). The tumor was completely removed (Fig. 2B), and postoperative visual improvement was temporarily observed.

**Pathological Examination.** Pathology revealed tumor cells with atypical nuclei of differing sizes and eosinophilic bodies (Fig. 2C). Nucleoli in hyperplastic cells and scattered necrotic foci were apparent, and mitotic cells were 5/10 hpf. The MIB-1 index with antibodies (M7240, 1:200; Dako) was 15.9% (Fig. 2D), p53-positive cells (clone DO-7 [M7001], 1:200; Dako) were 8.3% (Fig. 2E), and merlin was positive with A-19 antibody immunohistochemistry (sc-331, 1:50; Santa Cruz Biotechnology Inc.) (Fig. 2F). Because several CNAs detected by CGH were similar to that of the local recurrence, we concluded that the ON tumor was the disseminated lesion (Fig. 2H).

**Postoperative Course.** The ON tumor recurred and was removed 7 months after the third surgery. However, the patient’s condition worsened gradually, and she died 5.5 years after the initial surgery.

**Case 2**

**History.** This 70-year-old woman visited our hospital with rapidly worsening right blurred vision. She had undergone two total resections for a 6.0-cm left frontal tumor, one 6 years previously and the other (a local recurrence) 2 years previously (Fig. 3A and B). The pathological diagnosis was atypical meningioma because mitotic cells were 10/10 hpf. The MIB-1 index and p53-positive cell ratio were 19.0% and 7.9%, respectively. Copy number alterations detected by CGH were 1p, 10, 14q, 18q, 22q, and X losses (Fig. 4G).

**Examination.** The patient’s right eye barely exhibited light perception with tunnel vision (Fig. 3C). Brain MRI revealed a 0.9-cm mass adjacent to the right ON (Fig. 3D and E). The third surgery was performed via a frontotemporal craniotomy. The tumor, which was attached to the right ON surface, optic chiasm, and sellar diaphragm, severely compressed the right ON and was removed completely (Fig. 4A and B).

**Pathological Examination.** Studies revealed atypical cells with enlarged nuclei and whorl formation (Fig. 4C). Although mitotic cells were 1/10 hpf, atypical meningioma was confirmed because of increased cellularity, prominent nucleoli, and necrotic foci. The MIB-1 index and p53-positive cell ratio were 18.0% and 19.0%, respectively (Fig. 4D and E). Merlin was undetectable (Fig. 4F). The CGH profile was very similar to that of the previously resected tumor, and the ON lesion was confirmed to be a disseminated tumor (Fig. 4H).

**Postoperative Course.** After surgery, the patient’s vision was unchanged. Eight months after the final surgery, the tumor at the ON recurred, and Gamma Knife surgery was performed.

**Discussion**

We reviewed 38 cases of meningiomas with CSF dissemination previously reported in the literature. Among the 32 cases with a clearly identified primary site, 10 (31.3%) were intraventricular meningiomas. As is the case in glioblastomas, the proximity of the tumor to the ventricular system may increase the risk of CSF dissemination. The seeded sites were predominantly the spine and posterior cranial fossa. Ours is the first report of ON as the seeding site of meningiomas.

Copy number alterations, including 1p, 6q, 10, 14q, and 18q losses and 1q, 9q, 12q, 15q, 17q, and 20q gains, have been reported in atypical meningiomas and are associated with meningioma progression. Indeed, many unfavorable CNAs detected in the present cases were compatible with their aggressive clinical course. Interestingly, both disseminated tumors shared 1p and 10qcen-23 losses and 17q and 20q gains, suggesting that these chromosomal abnormalities may be among the risk...
factors of dissemination. These chromosomal regions encode molecules that were suggested to have a role in CSF dissemination. Hayashi et al. reported a significant association between a BCL10 single-nucleotide polymorphism on 1p22 and CSF dissemination in a limited series of intracranial germinomas. The protein encoded on BCL10 induces apoptosis and activates NF-kB. Kato et al. reported that mutations of the tumor suppressor PTEN on 10q23 were associated with dissemination in 39 glioblastomas. In medulloblastomas, 17q gain is associated with poor prognoses, and LASP1 on 17q12 plays a major role in dissemination. The protein encoded on LASP1 is an actin-binding protein possibly associated with cytoskeletal organization. Only one report of a disseminating meningioma included chromosomal analyses, and structural abnormalities, including unbalanced translocation t(1p15)(1q11), were reported with karyotyping.

Although the present cases lacked 22q, the expression of NF2, the major target of allelic 22q loss, was maintained in one case. Moreover, because 22q losses are similar among Grade I–III meningiomas, 22q loss is not thought to be associated with meningioma progression. Therefore, 22q or merlin loss, which is the product of NF2, is unlikely to have a role in dissemination.

Differences in CGH were observed for disseminated and locally recurring tumors. Although CNAs usually increase with progression, some CNAs in local recurrences were not observed in both cases. Selective pressure from different environments and constant instability throughout tumor progression may result in genetic changes in disseminated lesions, which could trigger the dissemination. In many studies, 20q gain, which was absent in

Fig. 2. Case 1. Intraoperative microscopic findings showing tumor within optic chiasm (arrow), left internal carotid artery (Lt IC), left anterior cerebral artery A1 segment (Lt A1), and right optic nerve (Rt ON) (A). The tumor was completely resected (arrowhead, B). Photomicrograph showing 5 mitoses in 10 hpf (arrow, C). The MIB-1 index was 15.9% (D). The p53-positive cell ratio was 8.3% (E). Merlin immunohistochemistry was positive (F). Comparative genomic hybridization profiles of the local recurrent tumor (G) and disseminated tumor (H). H & E, bar = 50 μm (C–F). Conf. = confidence.

Fig. 3. Case 2. Gadolinium-enhanced T1-weighted MR image at initial onset showing an enhanced frontal mass (A). Gadolinium-enhanced T1-weighted MR image demonstrating local recurrent tumor (B). Visual field examination showing extreme narrowing of right visual field (C). Gadolinium-enhanced T1-weighted MR image acquired after visual impairment showing a 0.9-cm mass attached to the right ON and diaphragm (arrowheads, D and E).
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the local recurrences but appeared in the disseminated tumors in both cases, was reported to be an important factor in colorectal carcinoma progression\(^1\)\(^2\) and could be associated with meningioma dissemination.

In conclusion, the genetic characteristics shared by these cases might be associated with CSF dissemination of meningiomas.

**Disclosure**

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

Author contributions to the study and manuscript preparation include the following. Conception and design: Kitamura. Acquisition of data: Kitamura. Analysis and interpretation of data: Kitamura. Drafting the article: Kitamura. Critically revising the article: Akiyama, Sasaki. Reviewed submitted version of manuscript: Akiyama, Sasaki, Hayashi. Study supervision: Yoshida.

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**References**


**Fig. 4.** Case 2. Intraoperative microscopic findings showing a tumor (arrow) compressing the right ON (A). The optic canal (OC) was drilled out, and the ON was released. Postoperative microscopic findings (arrowhead, B). Photomicrograph showing atypical cells with enlarged nuclei and whorl formation, and showing 1 mitosis per 10 hpf (arrow) (C). The MIB-1 index was 18.0% (D). The p53-positive cell ratio was 19.0% (E). Merlin was undetectable (F). Comparative genomic hybridization profiles of the local recurrent tumor (G) and disseminated tumor (H). H & E, bar = 50 μm (C–F).


