Usefulness of Intraoperative Photodynamic Diagnosis Using 5-Aminolevulinic Acid for Meningiomas with Cranial Invasion: Technical Case Report

Objective: We present a case of a meningioma in which photodynamic diagnosis (PDD) using 5-aminolevulinic acid was very useful in identifying the cranial involvement.

Clinical Presentation: An 83-year-old woman presented with a bony, hard, immobile bulge in her left forehead. Computed tomographic scans showed a thickening in the left frontal bone with a flat mass underneath. Magnetic resonance imaging scans revealed that enhancing lesions spread to the dura mater and subcutaneous tissue around the thickened frontal bone, reaching the upper margin of the left orbit.

Intervention: Intraoperative PDD using 5-aminolevulinic acid indicated the optimal extent of the excision by showing clear fluorescence of affected tissues. The tumor was totally resected and diagnosed as an atypical meningioma. Histopathological examination confirmed the consistency of the extent of tumor invasion with affected lesions on PDD.

Conclusion: To the best of our knowledge, this is the first case demonstrating the efficacy of PDD using 5-aminolevulinic acid for a meningioma with cranial invasion. Additional studies are warranted, as shown in cases of malignant gliomas.

Keywords: 5-Aminolevulinic acid, Cranial invasion, Intraoperative photodynamic diagnosis, Meningioma, Skull invasion

Photodynamic diagnosis (PDD) using 5-aminolevulinic acid (5-ALA) has been performed much more frequently in recent years and has become an important intraoperative technique. Because of its convenience and usefulness in the field of neurosurgery, PDD is being performed on patients with malignant gliomas at many institutions (2, 4, 7, 8, 9). However, to the best of our knowledge, there have been no studies on PDD using 5-ALA in patients with cranial lesions. Here, we present a case of a meningioma in which PDD using 5-ALA was very useful in identifying cranial involvement.

Clinical Presentation

An 83-year-old woman complained of headache and a bulge on the left side of her forehead. She had no notable medical history, including head trauma, and previous cranial magnetic resonance imaging (MRI) scans did not show any abnormalities. She was referred to our department in June 2006 because the subcutaneous mass (diameter, ~3 cm) had become painful. It was bony, hard, immobile, and not tender. Cranial computed tomographic (CT) scans showed well demarcated thickening in the left frontal bone and a flat mass exhibiting isodensity immediately underneath. Destruction of both the inner and outer tables of the cranium was confirmed. Contrast-enhanced MRI scans showed even enhancement spreading to the dura mater and subcutaneous tissue around the thickened bone, reaching the upper margin of the left orbit. Diffuse meningeal enhancement was also seen adjacent to the tumor (Fig. 1), suggesting a rapidly progressing meningioma. In order to determine the extent of tumor excision intraoperatively, PDD using 5-ALA was planned and written informed consent was obtained. The protocol of PDD using 5-ALA was approved by the Ethics Committee of Nagasaki University.
Intervention

Three hours before the induction of anesthesia, 20 mg/kg of 5-ALA was administered orally. The patient was kept in a dark room for 48 hours after drug administration to avoid possible skin phototoxicity. After the scalp incision was made, adhesion between the cranial lesion and galea was seen in the area of bone thickening. The cranial lesion, along with the dura mater, was excised as a single mass. Intraoperative PDD showed that the tumor itself was highly fluorescent, but that the dura mater surrounding the tumor was not (Fig. 2). PDD also clearly showed fluorescence from the dipole to the inner table at the stump of the upper orbital margin (Fig. 3), whereas no tumor invasion was observed microscopically. Drilling was performed until the fluorescence disappeared while preserving the outer table. Surgery was completed after confirming the absence of residual fluorescence in the surgical field. The patient was discharged in good health 9 days after surgery. MRI scans performed 9 months after surgery showed no evidence of tumor recurrence (Fig. 4).

Histology

The tumor on the medial surface of the dura mater grew in a turbinated or fascicular manner and obviously involved the cranium. Tumor cells densely existed from the dipole to the outer table of the cranium, and cellular atypia and nuclear fission were seen. The tumor was diagnosed as an atypical meningioma (World Health Organization Grade II). No tumor cells were seen in the surrounding dura mater, including the area where contrast enhancement was observed on preoperative MRI scans. Tumor cells did exist in the fluorescent orbit-
was needed, including the superior wall of the left orbit. By confirming the negative fluorescence within the surgical field, the tumor was completely excised. Histopathological examination confirmed that PDD accurately assessed the extent of cranial involvement of the meningioma. Although rapid intraoperative pathological diagnosis of bone lesions without demineralization was not technically feasible, the degree of bone invasion was easily assessed on PDD.

Linear thickening and contrast enhancement of the meninges adjacent to a meningioma have been called the “dural tail signs,” “dural thickening,” “flare,” or “meningeal sign.” However, the histological basis of the dural tail with a meningioma is not completely understood. In the present case, preoperative contrast-enhanced MRI scans showed an enhancement of the dura mater adjacent to the meningioma. During the operation, the tumor itself was strongly fluorescent, and the surrounding dura mater was not. Pathological examination confirmed the existence of tumor cells in the fluorescent area, but none were seen in the nonfluorescent dura mater. This suggests that PDD using 5-ALA is quite useful in determining the extent of dura mater involvement in meningioma surgery.

5-ALA has been reported to have several adverse effects, such as skin sensitivity (phototoxicity), nausea, vomiting, and transient liver dysfunction. 5-ALA also produces protoporphyrin IX, which may increase the risk of phototoxic skin reactions within 48 hours of induction. Therefore, after the administration of 5-ALA, we kept the patient in dark surroundings for 48 hours. Thus far, we have used PDD using 5-ALA with a low-dose regimen in 75 cases, but we have never experienced such serious adverse effects.

The reliability of PDD using 5-ALA has not been fully verified. Positive reactions to photosensitive materials in non-tumor tissue and 85% sensitivity in even malignant gliomas have been reported (1, 3, 5, 8). Nevertheless, to the best of our knowledge, this is the first case demonstrating the usefulness of PDD using 5-ALA for a meningioma with cranial invasion. PDD using 5-ALA is convenient and inexpensive, and, because most adverse reactions are avoidable, it may be applied in diagnosing brain tumors other than malignant gliomas.

REFERENCES

1. Boehncke WH, Rück A, Naumann J, Sierry W, Kaufmann R: Comparison of sensitivity towards photodynamic therapy of cutaneous resident and infiltrating cell types in vitro. Lasers Surg Med 19:451–457, 1996.
2. Haglund MM, Berger MS, Hochman DW: Enhanced optical imaging of human gliomas and tumor margins. Neurosurgery 38:308–17, 1996.
3. Kirdaite G, Lange N, Busso N, Van Den Bergh H, Kucera P, So A: Prototoporphyrin IX photodynamic therapy for synovitis. Arthritis Rheum 46:1371–1378, 2002.
4. Kowalczyk A, Macdonald RL, Amidei C, Dohrmann G, Erickson RK, Hekmatpanah J, Krauss S, Krishnasamy S, Masters G, Mullan SF, Mundt AJ, Sweeney P, Vokes EE, Weir BK, Wollmann RL: Quantitative imaging study of extent of surgical resection and prognosis of malignant astrocytomas. Neurosurgery 41:1028–1038, 1997.
5. Messmann H, Kullmann F, Wild T, Knüchel-Clarke R, Rüschoff J, Gross V, Schölmerich J, Holstege A: Detection of dysplastic lesions by fluorescence in a model of colitis in rats after previous photosensitization with 5-aminolavulinic acid. Endoscopy 30:333–338, 1998.
6. Moore GE, Peyton WT, French LA: The clinical use of fluorescein in neurosurgery. The localization of brain tumors. J Neurosurg 5:392–398, 1948.

7. Stummer W, Novotny A, Stepp H, Goetz C, Bise K, Reulen HJ: Fluorescence-guided resection of glioblastoma multiforme by using 5-aminolevulinic acid-induced porphyrins: A prospective study in 52 consecutive patients. J Neurosurg 93:1003–1013, 2000.

8. Stummer W, Stocker S, Wagner S, Stepp H, Frisch T, Goetz C, Goetz AE, Kiefmann R, Reulen HJ: Intraoperative detection of malignant gliomas by 5-aminolevulinic acid-induced porphyrin fluorescence. Neurosurgery 42:518–526, 1998.

9. Stummer W, Pichlmeier U, Meinel T, Wiestler OD, Zanella F, Reulen HJ: ALA-Glioma Study Group: Fluorescence-guided surgery with 5-aminolevulinic acid for resection of malignant glioma: A randomised controlled multicentre phase III trial. Lancet Oncol 7:392–401, 2006.

Acknowledgments

We thank Keisuke Tsutsumi, M.D., Kentaro Hayashi, M.D., Tomohito Hirao, M.D., Naore Kinoshita, M.D., and Keisuke Toyoda, M.D., for their help in preparing this manuscript.

COMMENTS

The authors discuss a case report of an 83-year-old woman with an anterior frontal fossa cranial base meningioma, for whom they used protoporphyrin 5-aminolevulinic acid (5-ALA)-induced fluorescence to detect the extent of tumor and cranial resection. This interesting technique seems to be reasonably specific for gross tumor tissue, and the authors provide histopathological confirmation that the nonfluorescent dura showed no tumor cells. However, they do not show definitive histopathological confirmation that all the fluorescent tissue was indeed tumor. Previous reports in malignant gliomas (1) have suggested that falsely negative fluorescence may be detected in areas of blood-brain barrier breakdown that are not gross tumor. As such, it remains unclear what the threshold for detection at the tumor margins are with this technique.

The goal of this case report, as of others before it, was to intraoperatively detect the extent of tumor infiltration to optimize tumor resection. The problem with using this technique, however, has been that all tumor cells do not take up the fluorescent dye and all the areas of fluorescence are not necessarily tumor cells. This fact has contributed to the failure of photodynamic therapy using porphyrins for malignant gliomas and will also limit the ability to use “photodynamic diagnosis” to delineate with real accuracy the extent of “gross total resection.” Furthermore, unlike infiltrating gliomas, meningiomas are relatively well circumscribed. Therefore, the added value of using photodynamic diagnosis to visualize meningiomas beyond the abnormalities that can already be seen under the operating microscope is unclear. Unlike gliomas, meningiomas and cranial lesions can be distinguished from normal surrounding tissues using the operating microscope. Usually, the neurosurgeon’s ability to detect changes in texture, color, and vascularity that characterize cranial base lesions from surrounding normal tissues using the operating microscope is much greater than the ability to do so for intrinsic brain tumors. The difficulty of resecting cranial base lesions is usually not due to lack of visualization of tumor cells, but usually due to the location of the tumor. Therefore, it is often the functional anatomy (i.e., proximity to cranial nerves or major blood vessels), rather than the presence/absence of microscopic tumor tissue, that guides cranial base surgeons in their resections.

Nevertheless, this report suggests that 5-ALA-induced fluorescence can be used in the case of meningioma with cranial invasion. The technique seems to be reasonably safe, and it could be moderately helpful for selected patients with such cranial base lesions. This single case report, however, is primarily of anecdotal interest. The clinical practicality of this application for cranial base tumors is far from being demonstrated.

Linda M. Liau
Los Angeles, California

Michael M. Haglund
Durham, North Carolina

Edward R. Laws, Jr.
Boston, Massachusetts

Joseph M. Piepmeier
New Haven, Connecticut

This is a report of the original use of 5-ALA as a diagnostic labeling tool for tumors. There have been previous case reports or small series of patients in whom 5-ALA was used to identify spinal cord tumors (1). The authors have put together a photodynamic diagnosis of a large cranial base meningioma. Because this article is a case report, we do not know the extent of staining in the entire tumor, and the authors did not do a blind analysis of samples taken from different locations which were positive or negative for labeling with 5-ALA. Overall though, it is a nice example of the possibilities of photodynamic diagnosis for cranial base tumors such as meningiomas, but additional studies are necessary to determine whether the staining accurately matches the actual tumor.

This article is well illustrated, and as a case report, makes a valuable contribution. Because of my prior experience with photoradiation therapy and detection of tumors with hematoporphyrin derivative, I had not been a prior advocate of 5-ALA fluorescent staining for the removal of parenchymal tumors. It seemed clear that tumor bulk would take up the photoactive dye in an inhomogeneous fashion and that infiltrating tumor cells that were partially protected by the blood-brain barrier often did not. Nonetheless, it is interesting to see how clearly tumor invading bone is identified by this technique. For that reason, I think this case report is of significant interest and may provide practical benefit.

This technique may prove to be useful. I am still not certain about the sensitivity and specificity of this technique, and a single case is not going to answer that question. However, bone invasion and hyperosmosis from meningiomas can be hard to detect during surgery. The authors should extend these studies to include more experience with other patients.

This is an interesting case report describing the use of photodynamic visualization with 5-ALA to guide resection of a meningioma invading the cranium. This technique has been described previously.
for gliomas wherein margins between tumor and brain are less well defined. The benefits of this technique in patients with meningiomas are marginal because the tumor interface with surrounding structures is usually easily discernible. Additional studies, however, may demonstrate its utility in patients with bone invasion such as the one in this case report.

Jeffrey N. Bruce
New York, New York

The authors have described the use of 5-ALA for “photodynamic diagnosis” to help in the excision of an invasive meningioma. The authors propose that the use of this technique helps to ensure that the resection has been complete. They are to be congratulated on this interesting report, although a single case report does not prove that use of this technique is superior to just a radical resection.

Andrew H. Kaye
Melbourne, Australia