Spinal Anaplastic Oligodendroglioma With Oligodendrogliomatosis: Molecular Markers and Management: Case Report

BACKGROUND AND IMPORTANCE: Spinal cord oligodendrogliomas are rare tumors, with a reported incidence varying between 0.8% and 4.7% of all spinal cord tumors and just over 50 cases reported in the literature. Of these, only 9 cases are histologically defined as anaplastic oligodendrogliomas, with few having complete molecular characterization. The diffuse tumor spread that can occur along the subarachnoid space with secondary invasion of the leptomeninges is called oligodendrogliomatosis and is associated with poor outcome.

CLINICAL PRESENTATION: A 68-year-old man with a history of lumbar stenosis status after lumbar decompression presented with new-onset right lower-extremity weakness. Magnetic resonance imaging demonstrated an intramedullary lesion from T9 to T12. During an attempted diagnostic biopsy, numerous intradural intramedullary lesions not present on magnetic resonance imaging were observed. Tissue biopsy demonstrated a 1p/19q-codeleted anaplastic oligodendroglioma with diffuse oligodendrogliomatosis. Postoperative treatment included 39.2-Gy radiation over 22 fractions from T1 to the bottom of the thecal sac with a boost to the T9-T12 area, the primary site of disease, to a total dose of 43.2 Gy in 24 fractions, followed by adjuvant temozolomide at a dose of 200 mg/m² on days 1 to 5 in a 28-day cycle. At the 1-year follow-up, the patient demonstrated moderate neurological improvement.

CONCLUSION: Management, prognosis, and use of molecular data in the decision-making algorithm for these patients are discussed, together with a review of all cases of primary intradural intramedullary spinal anaplastic oligodendrogliomas reported to date. Our study indicates that the combination of sequential treatment with radiation and temozolomide might provide a favorable outcome in the case of 1p/19q-codeleted spinal anaplastic oligodendrogliomas and that molecular analysis can be beneficial in guiding treatment strategies, although the impact of IDH mutations on these tumors is still unclear.

KEY WORDS: Diffuse leptomeningeal oligodendrogliomatosis, IDH1 wild type, 1p/19q codeletion, Spinal anaplastic oligodendrioglioma

Primary spinal anaplastic oligodendrogliomas (AOs) are exceedingly rare, with only 9 reported cases in the literature. Although treatment of spinal oligodendroglioma typically involves a combination of surgical resection, radiation therapy (RT), and chemotherapy, there are few data on long-term outcome with primary spinal AO. Molecular studies of spinal AO were seldom reported until recently. Only 1 case report exists describing a patient with primary spinal AO with 1p deletion who gained significant improvement from resection followed by temozolomide therapy.

Here, we report a 68-year-old man found to have a 1p/19q-codeleted, IDH1/2 wild-type primary spinal AO who achieved significant improvement from resection followed by temozolomide therapy.
improvement after partial resection, RT, and temozolomide. To the best of our knowledge, this is the first reported spinal AO molecularly characterized by the presence of 1p/19q codeletion with no evidence of an IDH1 or IDH2 mutation (IDH wild type). In addition, we performed next-generation sequencing (NGS) analysis of 50 genes, which, to the best of our knowledge, makes this the most comprehensive genetic characterization of a spinal AO to date.

CLINICAL PRESENTATION

A 68-year-old man with significant history of prostate cancer presented with a 1-month history of right leg numbness. He had a prior history of lumbar spine decompression for lumbar stenosis causing left leg numbness 1 year earlier. Review of systems revealed weight loss, numbness, lower-extremity weakness, gait imbalance, and falls to the extent that he required a cane or wheelchair for ambulation. On neurological examination, his upper extremities were at full strength without pronator drift. Upper-extremity reflexes were 1+ throughout. Upper-extremity sensation was intact. His right leg was at full motor strength. His left gastrocnemius muscle demonstrated minimal antigavity movement with significant atrophy. Distally, he maintained full motor strength in both lower extremities. Patellar reflexes were absent and Achilles reflexes were preserved bilaterally. He had decreased pinprick to the left and right sides and patchy nondermatomal distribution sensory loss in the left lower leg. His proprioception was intact, and there was no clonus. A thoracic spine magnetic resonance image (MRI) was obtained, which demonstrated a nonenhancing T2-hyperintense intramedullary lesion expanding the conus at T9 to T12. A subtle 1.2-cm extramedullary nodule at T11 was identified on retrospective review of preoperative MRI after diagnosis. MRI of the rest of the spinal axis and MRI of the brain did not show evidence of further tumor spread (Figure 1A-1D). Surgery was performed to obtain a tissue diagnosis and for potential resection. Although the preoperative imaging suggested the tumor to be intradural and intramedullary at T9 to T12, when the dura was opened, clusters of tumor nodules were noted densely adherent to left- and right-sided nerve roots in the intradural extramedullary space (Figure 2). There was also subpial involvement of disease bilaterally and near the dorsal midline. Partial piecemeal resection of the largest epidural focus of the tumor was completed with the use of motor and somatosensory evoked potential monitoring. Because the smaller nodules did not appear on preoperative imaging, we were unable to estimate the true superior-inferior extent of the tumor. Coupled with our concern for intramedullary involvement, further resection, which would be a subtotal resection, posed an unnecessary risk of neurological deficits and therefore was halted.

Postoperatively, the patient received 39.6 Gy in 22 fractions of proton radiation from T1 to the bottom of the thecal sac followed by a boost to the T9-T12 area to a total dose of 43.2 Gy in 24 fractions to the primary site of disease followed by adjuvant temozolomide at a dose of 200 mg/m² on days 1 to 5 in a 28-day cycle. MRIs of the spine after radiation and after 8 cycles of adjuvant temozolomide showed improvement in enhancement and a T2 signal abnormality within the cord at T11 consistent with response to treatment or improvement in radiation-related change (Figure 3). There are no signs of disease recurrence, and he experienced moderate clinical improvement in lower-extremity strength. MRI of the brain once again did not show evidence of cranial involvement. Clinically, at the 1-year follow-up, the patient demonstrated left lower-extremity strength of 3/5 in hip flexion, 5/5 strength in knee extension, 4/5 knee flexion, and 3/5 strength in ankle dorsiflexion; great toe dorsiflexion; and ankle plantar flexion. Right lower-extremity strength was 5/5 throughout. Sensation was intact to light touch except for a mild decrease over the left lateral thigh. There was no evidence of ankle clonus bilaterally. The patient is receiving physical therapy and reports being able to ambulate with a single-point cane and occasionally a knee brace for the left knee to prevent hyperextension. Assessment of urinary function is confounded by the history of prostate cancer.

After completion of radiation, the patient was treated with adjuvant temozolomide 150 mg/m² on days 1 to 5 in a 28-day cycle for the first cycle, which was increased to 200 mg/m² beginning with the second cycle. To date, he has completed 12 cycles of adjuvant temozolomide with overall good tolerance to therapy and no evidence of tumor progression. He is currently on surveillance.

Pathological Studies

Biopsy materials were submitted for cytologic smear preparations and frozen section (fresh), routine light microscopy (formalin fixed), and electron microscopy (glutaraldehyde fixed). Formalin-fixed paraffin-embedded tissue was cut at 4 to 6 μm for hematoxylin and eosin-stained sections and for immunohistochemical studies. Immunohistochemical studies were performed on Leica immunostainers (Leica Biosystems, Buffalo Grove, Illinois). These included antibodies to Ki-67 antigen (Dako, clone MIB-1, 1:100 dilution), phospho-histone H3 (Upstate Biotechnology, Millipore, rabbit polyclonal, 1:400 dilution), glial fibrillary acidic protein (BD Biosciences, 4A11, clone 1B4, 2E1, 1:7000), S-100 (BioGenex, clone 15E2E2, 1:900), synaptophysin (Novocastra, clone 27G12, 1:600), Neu-N (Bio SB, clone A60, 1:50), and IDH1 R132H (Dianova, clone H09, 1:40).

Tissue submitted to the Electron Microscopy Section of the Department of Pathology at Texas Children’s Hospital was fixed in Trump glutaraldehyde, osmicated, dehydrated, and embedded in resin. Thin sections were stained with uranyl acetate and lead citrate. Representative electron microscopy images were prepared for review.

Cytologic examination demonstrated monomorphic-appearing tumor cells with finely granular chromatin and small nucleoli. Cell processes were scant. Occasional pleomorphic nuclei were seen. Thin-walled capillaries were prominent on smear preparations (Figure 4A). Low-power microscopic examination demonstrated the same monomorphic tumor cells with perinuclear cytoplasmic clearing and a delicate capillary network (Figure 4B and 4C).
Some portions of tumor appeared to infiltrate native parenchyma, indicated by the presence of neuropil, morphologically normal neurons (Figure 4D, arrow), and corpora amylacea. The demarcation between tumor in the subarachnoid space and within cord parenchyma was ill-defined.

The tumor was proliferative with a mitotic rate of up to 4 per 10 high-power (×40) fields (Figure 4E demonstrates phosphohistone H3 staining of mitoses). A correspondingly high proliferation index of 18.7% was found on automated quantitation of Ki-67 antigen labeling (1000 nuclei counted). Neither
microvascular proliferation nor tumor necrosis was seen. Additional pertinent negative findings included the absence of rosettes and morphologically abnormal neurons.

Immunohistochemical studies demonstrated that tumor cells were glial fibrillary acidic protein negative and strongly S-100 positive (Figure 4F). Neu-N immunostain highlighted the neurons surrounded by infiltrating tumor cells. Neurofilament stain demonstrated dot-like perinuclear immunoreactivity (Figure 4H), and cells were negative for IDH1 R132H mutant protein (Figure 4I).

Electron microscopy did not reveal evidence of neuronal differentiation such as neurosecretory vesicles.

Fluorescence in situ hybridization studies for 1p/19q status were performed on unstained formalin-fixed paraffin-embedded sections with LSI 1p36, LSI 1q25, LSI 19q13, and LSI 19p13 dual-color probes (Abbott Molecular, Inc). The 1p36/1q25 and 19q13/19p13 signal ratio cutoffs for 1p and 19q deletion were set at <0.8. NGS-based analysis was performed to detect mutations in the coding sequences of 50 genes, including BRAF, CDKN2A, EGFR, IDH1, IDH2, KRAS and NRAS, PIK3CA, PTEN, and TP53.

Codelletion of 1p and 19q was identified in the tumor (1p/1q ratio, 0.66; 19q/19p ratio, 0.65), as well as monosomy of chromosome 1. The NGS-based analysis did not identify somatic mutations in any of the 50 genes tested. Because of the rarity of the molecular profile, we used residual tissue from the patient’s tissue block to retest for IDH1 and IDH2 mutations by NGS and 1p/19q codelletion by fluorescence in situ hybridization. A result similar to the original one was obtained with no evidence of mutations in exomes 4 of IDH1 and IDH2 and codelletion of 1p/19q.

**DISCUSSION**

Primary tumors of the spinal cord are rare, and only 2.5% are diffuse gliomas. Although histopathology is still the gold standard for the classification of gliomas, it is increasingly clear that the histopathological diagnosis lacks the precision needed for tailored treatment of individual patients. The typical molecular signature of oligodendrogliomas is the combined loss of genetic material from chromosomal arms 1p and 19q, resulting in an unbalanced translocation that leads to loss of heterozygosity. However, the assessment of this and other molecular markers has not been routinely implemented in clinical practice until recently because of the lack of therapeutic implications. In fact, this marker was considered to be prognostic regardless of whether patients were receiving RT, chemotherapy, or both. In 2012, the situation changed with the publication of the long-term follow-up results of the Radiation Therapy Oncology Group 9402 and European Organisation for Research and Treatment of Cancer 26951 trials, confirming not only the prognostic but also the predictive value of 1p/19q codeletion. Both trials showed a significant overall survival benefit (doubling of survival) from the addition of upfront chemotherapy with procarbazine, lomustine, and vincristine (PCV) to RT in patients with intracerebral pure and mixed anaplastic oligodendrogliat tumors with 1p/19q codelletion, whereas for those with tumors without codelletion, there was no difference in median survival by treatment arm. Whether temozolomide, a newer alkylating agent with a better safety profile, is equivalent in efficacy to PCV is currently unknown, although van den Bent et al showed a 52.6% response rate to temozolomide in chemotherapy-naive patients with recurrent cerebral oligodendrogliomas.

There is a strong association between IDH mutations and 1p/19q codelletion in AO. Most (90%-100%) 1p/19q codelleted cerebral gliomas also have IDH1/2 mutations, and the presence of IDH1 mutations predicts improved survival in higher-grade gliomas. There is now also some evidence that, besides being prognostic, the presence of IDH1 mutation can be predictive of a response to chemotherapy in patients with intracerebral AO, as shown by the reanalysis of data from RTOG 9402. However, the frequency of IDH mutations seems to be different in spinal AOs, and the prognostic and predictive implications are unknown. In a single-institution retrospective analysis, Ellezam et al found that 9 spinal cord gliomas (3 diffuse astrocytomas, 2 World Health Organization grade 2 oligodendrogliomas, and 4 anaplastic astrocytomas), none were IDH1 mutated by immunohistochemistry. Furthermore, the study included a total of 44 patients with tumor, all of whom had infratentorial or spinal cord grade 2 and 3 diffuse gliomas. Of these patients, only 7% were positive for IDH1 mutation, all localizing to the brainstem. The tumor discussed in this case was also negative for IDH1 or IDH2 mutation by immunohistochemistry and molecular sequencing.

The lack of IDH1 mutations occurring with the 1p/19q codelletion in the spinal cord glioma population differs strongly from similar-grade tumors of the supratentorial region. The European Organization for Research and Treatment of Cancer Brain Tumor Group reports that IDH1 mutation are found in 55% to 80% of grade 2 and 3 gliomas. In confirmed AO cases, about half had the IDH1 mutation, with combined 1p/19q
codeletion in 86%.\textsuperscript{14} Schniederjan et al\textsuperscript{15} presented 9 pediatric patients with diffuse leptomeningeal neuroepithelial tumor, known to have pathological features similar to those of oligodendroglioma, in whom none of the tumors were reactive with IDH1 antibodies. This further underscores the point that although IDH1 mutations are often associated with 1p/19q codeletion, almost always associated with a TERT promoter mutation and frequently associated with CIC mutation. Type 2 designates IDH mutation without 1p/19q codeletion. Type 3 refers to the IDH wild type, and this category is further subdivided into type 3a for grade 2 tumors and type 3b for grade 3 tumors. Whether this molecular classification can be extrapolated to include spinal gliomas is unclear. In fact, our patient would not fall under any of the above 3 types because in the Suzuki et al study all type 3 tumors that were IDH wild type were also 1p/19q intact. Of note, TERT status and CIC status are not included in the MD Anderson Cancer Center NGS.

The benefits of RT and chemotherapy in spinal AOs are unknown because of the low incidence of these tumors. Because only 9 cases of spinal AOs have been described in the literature, the assumption is made that spinal AOs respond to treatment similarly to cerebral oligodendrogliomas.\textsuperscript{1} Nam et al\textsuperscript{17} used RT to treat a 38-month-old boy with spinal AO. No evidence of recurrence was noted at 48 months. In the 1 case in the literature of a spinal AO with molecular data showing the presence of 1p deletion, the

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\caption{Postoperative magnetic resonance imaging study of the spinal lesion. A, sagittal T2 image at T9 through T12-L1 disk space obtained May 2014 after surgery and before further treatment. Expansion of the cord focally associated with T2 hyperintensity is seen at T9-T10 through T11-T12. There was no abnormal enhancement. B, sagittal T2 image at T9 through T12-L1 disk space obtained May 2015 after chemoradiation. Expansion of the cord has nearly resolved. T2 hyperintensity appears more limited in extent, now confined to T10 to T11 levels. C, axial T2 image through the T11-T12 disk space, May 2014. Postoperative change of laminectomy is seen. Expansion and T2 hyperintensity of the cord are well delineated. D, axial T2 image through the T11-T12 disk space, May 2015. Mild residual expansion and faint T2 hyperintensity are visible, significantly improved from May 2014.}
\end{figure}
patient’s tumor responded clinically and radiographically when treated with temozolomide at recurrence. A good response was also seen in a patient described by Guppy et al., who treated a spinal grade 2 oligodendroglioma with 1p/19q codeletion and cerebral oligodendrogliomatosis with temozolomide. Michotte et al. reported a 1p/19q–codeleted leptomeningeal AO that responded favorably to temozolomide.

Our review of the English literature produced 9 reported cases, ours being the 10th case, of primary spinal AO (Table). Wang et al. reported the only other spinal AO with 1p/19q codeletion that underwent partial resection and temozolomide and experienced a positive outcome at 12 months. The majority of cases have incomplete follow-up data, or the patient died within 6 months. All cases underwent biopsy or partial resection followed by radiotherapy, with the exception of the study by Fountas et al., which did not use postoperative radiation. Ramirez et al. reported on a partial resection followed by adjuvant PCV, but the patient was found to have brain metastases at 19 months.

In contrast to spinal AO, diffuse leptomeningeal oligodendrogliomatosis (DLO) is a unique pathological entity diagnosed in the spinal cord with very few cases reported. The true number of primary DLO is likely overestimated, as a comprehensive surgical, radiologic, and pathologic evaluation is necessary to exclude a primary, intraparenchymal focus of tumor that has given rise to disseminated leptomeningeal
tumor, as in our case. The presentation of DLO varies, but typical symptoms are derived from hydrocephalus or mass effect. Unlike intracerebral oligodendroglioma, calcifications are rarely reported in DLO.

Prognosis is generally poor, with survival in the reported cases ranging from months to years. One case of DLO with 1p deletion has been reported to have a favorable response to PCV followed by temozolomide.

Because our patient had oligodendrogliomatosis, surgery was done only for diagnostic purposes. In the literature, a gross total resection was possible in only 15.7% of spinal oligodendrogliomas owing to the infiltrative nature of these tumors. To date, only a single report of a primary spinal AO with 1p deletion benefiting from temozolomide exists. Without any large studies examining the efficacy of temozolomide in this tumor population, management is currently guided by data acquired in the management of intracranial AO with hopes that an accurate extrapolation is possible.

CONCLUSION

Spinal oligodendroglioma remains a rare diagnosis with very limited molecular data reported. In this report, we have described the radiologic, intraoperative, pathologic, and molecular features of an intramural and intramedullary spinal AO with extradural seeding. We have also described the surgical and oncologic management of this patient, including partial resection followed by RT and temozolomide. Our study indicates that the combination of sequential treatment with radiation and temozolomide might provide a favorable outcome in the case of 1p/19q-codelleted spinal AOs and that molecular analysis can be beneficial in guiding treatment strategies, although the impact of IDH mutations on these tumors is still unclear. The results of NGS analysis confirm earlier reports that spinal oligodendrogliomas are frequently IDH wild-type and extend this finding by demonstrating wild-type sequences in 48 additional genes that are commonly mutated in human cancers.

Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

REFERENCES


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