

Leptomeningeal Oliogodendrogliomatosis Despite IDH1 Mutation, 1p/19q Codeletion, and MGMT Promoter Methylation

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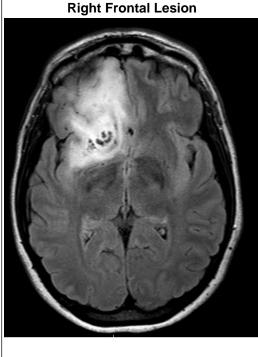
Introduction

Oligodendroglioma is a low grade glioma (LGG) comprising approximately 5% of gliomas. The paradigm that primary central nervous system (CNS) tumors, specifically these LGG are restricted to local advancement rather than metastatic spread of disease has been challenged by several reports demonstrating both disseminated CNS and even distant corporal metastases by primary anaplastic oliogodendrogliomas.

Over the past decade, molecular and genetic characterization of tumor specimens has become a commonplace, nearly defining, feature of newly diagnosed LGG. The 1p/19q, Isocitrate Dehydrogenase 1 (IDH1) mutation, and methylation of the O6-methylguaninemethyltransferase (MGMT) promoter are genetic changes associated with improved progression-free survival.

Methods

Our case is the first report of leptomeningeal spread and distant CNS metastasis of an oligodendroglioma despite favorable genetic subtyping, including IDH1 mutation, 1p/19g codeletion, and MGMT promoter methylation. This unique case prompted a review of the literature, which identified several salient features about our case, which have also been identified as risk factors for LGG progression, including initial tumor size and subtotal resection. Futhermore, we requested analysis of our tumor specimen for additional genetic mutations not yet applicable in clinical practice.



This axial FLAIR preoperative image demonstrates a right frontal, partially calcified oligodendroglioma.

Results

Our cranial specimen and spinal metastatic lesion continued to demonstrate favorable mutations at IDH1, 1p/19q (codeletion), and MGMT promoter.

Analysis performed by Foundation Medicine identified mutations of the following genes in the surgical specimen collected from this patient's initial tumor resection in 2009:

 TERT_c.124 C>T; TERT promoter gene, involved in the regulation of telomerase activity, activation by this mutation may lead to cellular omnipotence.



An expansile, mildly enhancing mass was identified in the lower thoracic spinal cord on post-contrast T1-weighted MRI. On biopsy, this lesion was found to be oligodendroglioma.

- MED12_c.128A>C; mutation may alter regulatory cascade of gene transcription.
- CDK12_c.3399A>T; Cyklin-dependent kinase 12 maintains genomic stability by regulating expression of DNA damage repair genes.

- CDH20_c.1925T>C; one of many calcium-dependent adhesion molecules which form cell junctions. Mutations in cadherin genes have been associated with increased frequency of metastasis.
- FRS2_c.1177G>A; Fibroblast growth factor receptor substrate 2; involved in neurogenesis in pluripotent cells, and in angiogenesis in mature cells.
- RET_c.1699G>A; normally involved in cell signalling. RET mutations may be involved in the development of many cancers via unregulated cellular growth. This specific RET mutation has not been associated with the MEN-2 syndrome.

Conclusions

Both genetic and surgical factors are associated with metastatic spread of low grade glioma. As more patients survive late into their disease thanks to adjuvant treatment, previously rare sequelae, including metastasis, is increasingly reported. Thus, further research is needed to identify a molecular signature of low grade lesions with greater metastatic potential.

References

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