

## The Co-Occurrence of Astrocytoma and Neuromyelitis Optica Spectrum Disorder in a Child-A Diagnostic Dilemma

Sudarshawn Damodharan<sup>1</sup>, Chrysanthy Ikonomidou<sup>3</sup>, Susan L Rebsamen<sup>4</sup>, Shahriar M Salamat<sup>5,7</sup>, Kristin A Bradley<sup>6</sup>, James A Stadler<sup>7</sup>, Kristin T Casey<sup>2</sup>, Neha J Patel<sup>2\*</sup>

<sup>1</sup>Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

<sup>2</sup>Division of Pediatric Hematology, Oncology and Bone Marrow Transplant, Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

<sup>3</sup>Section of Pediatric Neurology, Department of Neurology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

<sup>4</sup>Section of Neuroradiology, Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

<sup>5</sup>Department of Pathology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

<sup>6</sup>Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

<sup>7</sup>Department of Neurological Surgery, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

\*Corresponding author: Neha Patel, Division of Pediatric Hematology, Oncology and Bone Marrow Transplant, Department of Pediatrics, University of Wisconsin, 1111 Highland Ave., MC WIMR 4105, Madison, WI 53705, USA, Tel: 6082636420; E-mail: npatel@pediatrics.wisc.edu

Rec date: August 23, 2018; Acc date: September 19, 2018; Pub date: September 25, 2018

Copyright: © 2018 Damodharan S, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Citation: Damodharan S, Patel NJ, Casey KT, Ikonomidou C, Rebsamen SL, et al. The Co-Occurrence of Astrocytoma and Neuromyelitis Optica Spectrum Disorder in a Child-A Diagnostic Dilemma. J Neurooncol Neuroscience. 2018, Vol.3 No.1:3.

### Abstract

Astrocytomas (ACs) are common central nervous system (CNS) neoplasms in the pediatric population. Neuromyelitis optica spectrum disorder (NMOSD) is a rare autoimmune demyelinating childhood condition affecting the CNS. This case represents the first known co-occurrence of both of these disease processes in a pediatric patient. Both conditions have overlapping neurologic symptoms and radiographic features that could potentially mimic one another. Our patient initially presented with a seizure with brain imaging confirming a mass within her left frontal lobe. Surgical resection of the mass was done with histopathology significant for a high-grade astrocytoma, which our patient received treatment for with chemo-radiotherapy. Later, her symptoms progressed to involve acute onset vision loss in her left eye causing our differential diagnosis to expand and leading to confirmation of NMOSD. Subsequent immunosuppressive treatments led to complete restoration of her vision and resolution of her neurologic symptoms. Consequently, the initial diagnosis was revisited and changed to a concurrent low-grade astrocytoma and NMOSD through extensive evaluation and testing.

**Keywords:** Autoimmune neuromyelitis optica; Diffuse astrocytoma; High-grade glioma; Optic neuritis; Demyelination; Pediatrics

**Abbreviations:** AC: Astrocytoma; ACs: Astrocytomas; AQP4: Aquaporin-4; ATRX: Alpha-thalassemia X-linked intellectual disability syndrome; CD 68: Cluster of Differentiation 68; CNS: Central nervous system; CSF: Cerebrospinal fluid; ED: Emergency department; EEG: Electroencephalogram; IDH1: Isocitrate dehydrogenase enzyme isoforms 1; IDH2: Isocitrate dehydrogenase enzyme isoforms 2; IV: Intravenous; MOG: Myelin oligodendrocyte glycoprotein; MRI: Magnetic resonance imaging; NMO: Neuromyelitis optica; NMOSD: Neuromyelitis optica spectrum disorder; UCSF: University of California, San Francisco; WHO: World Health Organization.

### Introduction

Astrocytomas (ACs) are the most prevalent central nervous system (CNS) tumor in children that differentiate from a particular type of glial cell line in the cerebrum called astrocytes [1,2]. These heterogeneous neoplasms are typically graded utilizing the World Health Organization (WHO) grading system from I to IV based upon the degree of tumor cell anaplasia and invasiveness [2]. Most pediatric ACs are classified as low-grade (WHO grade I and II) with superior outcomes to those of high-grade (WHO III and IV) [1].

Neuromyelitis optica (NMO) and neuromyelitis optica spectrum disorder (NMOSD) are autoimmune conditions that cause severe inflammation and immune-mediated demyelination of the CNS [3,4].

The co-occurrences of ACs and autoimmune demyelinating processes such as NMO/NMOSD is uncommon, and to date there have been no reported pediatric cases of this presentation. This report presents the first known case of a pediatric patient with co-existent astrocytoma along with NMOSD.

## Case Report

An 8-year-old African American female presented to the emergency department (ED) following a generalized seizure. Seizure semiology was not witnessed, however her mother found her to be foaming from the mouth, unresponsive, with urinary incontinence. Her past medical history was significant for multiple prior partial complex seizures, learning disability, and poorly controlled asthma. Family history was significant for epilepsy in her father, learning disability in her mother, metastatic colon cancer in her maternal grandmother, and multiple family members with autoimmune conditions on her maternal side.

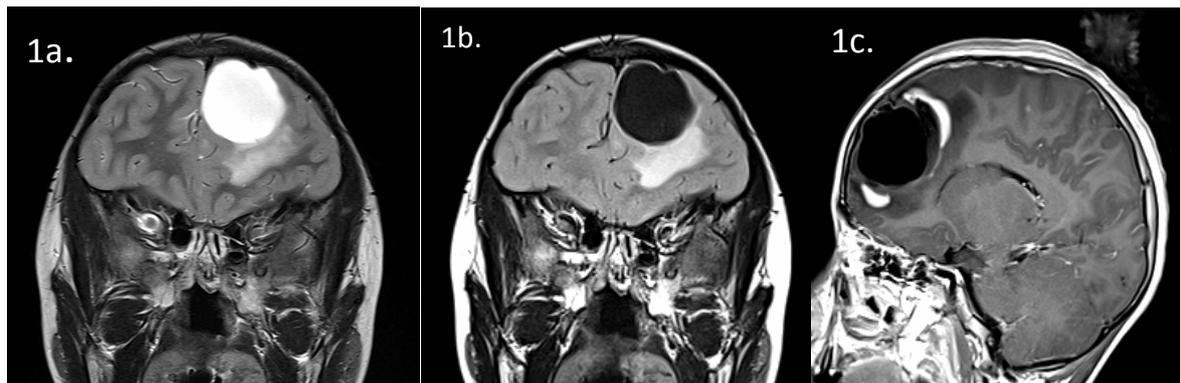
In the ED, our patient was awake and alert but appeared tired. Vitals obtained were within normal limits and the patient was afebrile. No significant neurologic deficits were noted on physical exam. Baseline electrolytes complete blood counts, and blood glucose were normal.

On admission, video electroencephalogram (EEG) performed was significant for an epileptogenic focus over the left frontal lobe and our patient was started on Levetiracetam for anti-seizure prophylaxis. Magnetic resonance imaging (MRI) of the brain revealed a partially solid and partially cystic mass within the left frontal lobe with ring enhancement and

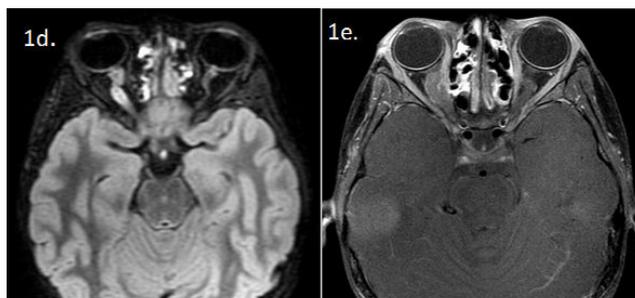
edema (**Figure 1**). Additionally, the imaging showed that there were two additional foci of enhancement within the posterior subcortical white matter in the left superior and left inferior frontal gyri and abnormal T2-weighted hyperintensity within the right pre-chiasmatic optic nerve with subtle contrast enhancement. MRI of the spine was unremarkable.

The patient underwent a left frontal craniotomy with intraoperative pathology demonstrating an astrocytoma, and gross total resection of the primary enhancing mass was achieved without complications or postoperative deficits. Pathologic studies from the mass were reported as a WHO Grade III anaplastic astrocytoma. CD68 immunohistochemistry revealed mainly perivascular macrophages with some activated microglia that was initially interpreted as reactive changes in an anaplastic neoplasm (**Figures 2 and 3**). Isocitrate dehydrogenase enzyme isoforms 1 (IDH1) and 2 (IDH2) were wild type and not significant. O(6)-methylguanine-DNA methyltransferase methylation was not detected. There was diffuse and strong nuclear immunoreactivity with ATRX antibody while the tumor cells revealed absent nuclear immunoreactivity with p53 antibody.

Further treatment for the anaplastic astrocytoma consisted of a multimodal approach of radiotherapy and chemotherapy. The patient went on to receive six weeks of concurrent radiochemotherapy with minimal complications. A few months had passed since our patient's initial presentation and prior to the start of her maintenance phase chemotherapy she began to complain of significant memory loss that had not been noted on prior follow-up visits. This was then followed a few days later by an acute onset of vision loss and pain in her left eye.



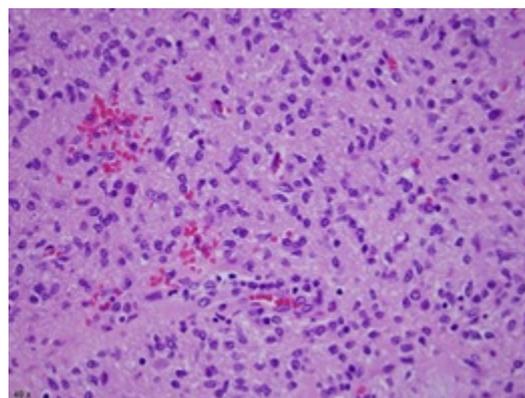
**Figure 1** a) T2 Coronal b) T2 Flair Coronal and c) Post Enhanced Axial images demonstrate a cystic mass with adjacent edema within the left frontal lobe with enhancement at the posterior superior and anterior inferior border margins of the cyst.



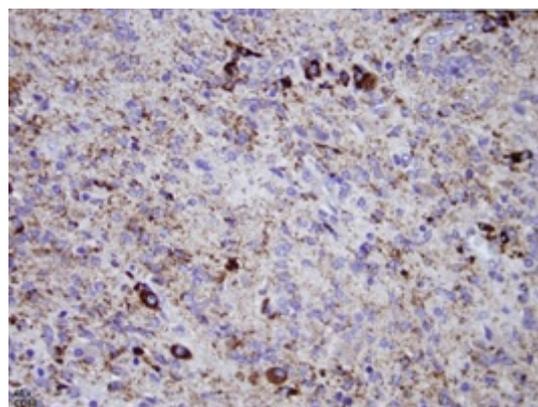
**Figure 1** d) T2 Flair Axial and e) Post Enhanced T1 Axial with Fat Suppression images demonstrates additional abnormal T2 Flair signal with enlargement and enhancement involving the right intraorbital optic nerve.

Our patient was once again admitted to the hospital with follow up brain MRI done which showed new small lesions on T2-weighted imaging with punctate foci of enhancement scattered throughout the cerebral hemispheres, the pons, and bilateral optic nerve changes (**Figure 4**). Given these findings, the differential at the time was thought to be tumor progression versus an inflammatory and/or demyelinating process. A lumbar puncture was performed with cerebrospinal fluid (CSF) and serological studies sent for potential infectious and autoimmune etiologies for her symptoms. Given our patient's continued left eye vision loss and increasing pain, it was decided to acutely start her on high dose intravenous (IV) corticosteroids to treat her likely inflammatory process. She had a dramatic response to the corticosteroid treatment with rapid recovery of her vision.

The analysis of the CSF returned positive for titers of myelin oligodendrocyte glycoprotein (MOG), which was consistent with the diagnosis of NMOSD. Our patient continued on a corticosteroid regimen and was started on additional immunosuppressive therapy with periodic rituximab infusions. Pathology from her original tumor resection was reexamined with findings consistent with a concurrent demyelinating process in addition to the atypical astrocytes previously noted (**Figure 5**). Molecular profiling using 500 cancer-associated genes on our patient's tumor tissue was performed. This found alterations in genes that are involved in the Ras-Raf signaling pathway that are frequently seen with low-grade astrocytomas [5].



**Figure 2** Hematoxylin and Eosin stained section of the lesion reveals a hypercellular process, including a mixture of glia with nuclear atypia, microglia and macrophages (40x original magnification).



**Figure 3** CD68 immunohistochemistry confirms presence of macrophages and microglia in areas of hypercellularity (40x original magnification).

After a thorough review of the molecular pathology and taking into account the demyelinating process, our patient's final oncologic diagnosis was a WHO Grade II diffuse astrocytoma. The higher proliferative index seen was thought to be secondary to a reactive, inflammatory process due to the concomitant autoimmune NMOSD.

Our patient is currently doing well and is no longer receiving therapy directed towards her astrocytoma with no evidence of recurrence on surveillance imaging. She remains on a regimen of corticosteroids and rituximab for her NMOSD with continued follow up, imaging, and serial exams.

## Discussion

ACs are the most common pediatric brain tumor and account for more than half of all primary CNS malignancies [1,2]. Initial presenting symptoms are non-specific and location-based. This includes increased intracranial pressure, cerebellar dysfunction, seizures, motor deficits, visual

impairment, and behavioral changes [2,6]. NMO and NMOSD are both uncommon in the pediatric population with an incidence of approximately five percent of all confirmed NMO/NMOSD diagnoses [3,4]. Typical presentation of these diseases includes visual loss, limb weakness, and possible bladder dysfunction secondary to the immune mediated CNS inflammation and demyelination [3,4]. The diagnosis of NMO/NMOSD has been debated in the past, but now typically involves imaging consistent with a demyelinating process along with CSF analysis for disease specific NMO-IgG antibodies; aquaporin-4 (AQP4) and MOG [4]. As stated, our patient represents the first known pediatric case of a concomitant astrocytoma with confirmed NMOSD that presented various dilemmas during her course.

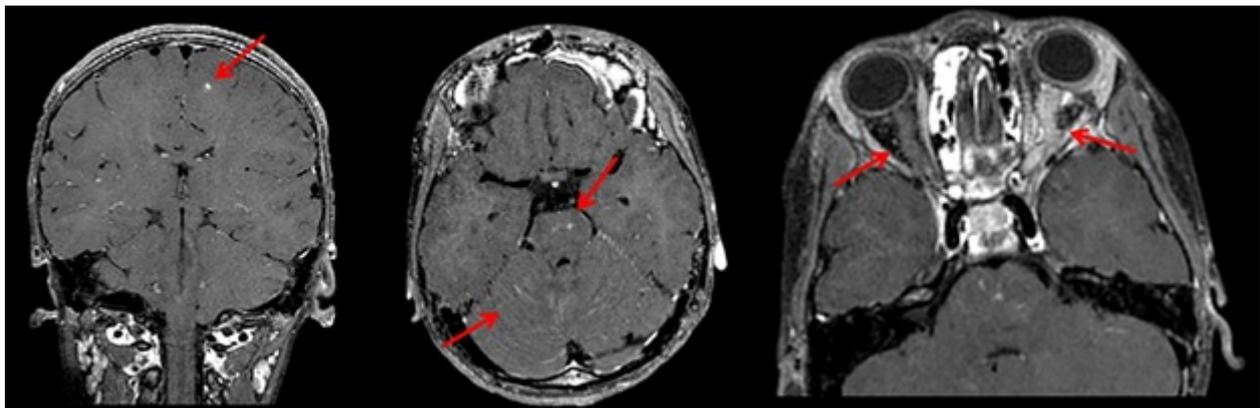
Our patient's presentation with symptoms of acute left eye pain and vision loss after her tumor resection was what led to the expansion of the differential diagnosis and diagnostic workup. This was due to the fact that this would have been an atypical presentation for a high-grade astrocytoma or a complication from radiotherapy as the lesions seen on imaging at the time of this presentation occurred outside the tumor location and radiotherapy field. Thus, the CSF analysis concluded that she had NMOSD and was suffering from optic neuritis. She was then started on appropriate treatment of her inflammation to relieve her symptoms with an excellent response.

With our patient now having confirmed NMOSD, this led to a reevaluation of the initial tumor tissue as it brought into question whether our patient had even had an oncologic process or was this all just an atypical presentation of a

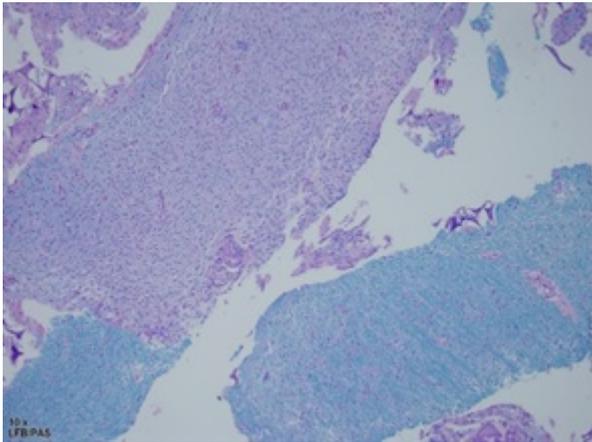
demyelinating process. On pathology, the dilemma arises in that both tumor and autoimmune demyelinating processes demonstrate increased cellularity and proliferation, therefore, occasionally making it difficult to recognize the co-existence of both processes in the same biopsy [7,8]. Though atypical astrocytes were present, there are no definitive markers at this time to help identify a neoplastic astrocyte in a mixed disease process. For this reason, the 500-cancer gene panel testing was performed to further categorize our patient's presumed tumor given her atypical clinical course.

The purpose of the 500-cancer gene panel test is to identify genetic mutations within tumor cells that could potentially lead to targeted therapies to combat a patient's cancer [7]. Additionally, the test results could also provide information on the risk of a patient, or members in their family, developing cancer based upon genetic changes that are shown [5]. For our patient, the genetic mutations that returned were consistent with those of a low-grade astrocytoma helping us confirm the oncologic diagnosis in addition to her autoimmune demyelinating process.

In this case, the challenges faced caused questions to arise that led to our patient's correct diagnoses and treatment modalities. Given that our patient's low-grade astrocytomas does have the potential to become high-grade and the genetic mutations found on her tumor gene panel testing may put her at an increased oncologic susceptibility, close monitoring and surveillance will continue. Her NMOSD will also continue to be followed closely and treated as needed with corticosteroids and immunosuppressive therapies.



**Figure 4** 3D-T1 Post Enhanced in a) coronal and b) axial planes demonstrate additional enhancing foci within the pons, cerebellum, and supratentorial white matter. c) Note the improvement in the enhancement of the right optic nerve, but the interval development of new enlargement and enhancement of the left optic nerve.



**Figure 5** A LFB/PAS stain for myelin reveals severe loss of myelin and pallor, in a white matter fragment that is infiltrated by macrophages, microglia and gliosis, as compared to two white matter fragments that are not appreciably demyelinated (10x original magnification).

## Conclusion

The concomitant occurrence of an astrocytoma with a demyelinating process is extremely rare and our patient represents the first reported pediatric case consistent with a low-grade astrocytoma with confirmed NMOSD. Atypical patient presentations should raise the suspicion of clinicians to investigate further for the potential of multiple disease entities. As research continues to advance, it will become easier to differentiate and diagnose diseases with similar symptoms and presentations. In the meantime, clinical curiosity must always persist especially when new developments in a patient's course come about.

## Acknowledgements

We would like to thank Dr. Arie Perry, neuropathologist from the University of California, San Francisco (UCSF) for the detailed second review of the pathology and his assistance in resolving this diagnostic dilemma. We would like to also thank Dr. David Solomon from the department of pathology, division of neuropathology, UCSF for his molecular profiling.

## References

1. Baker SJ, Ellison DW, Gutmann DH (2016) Pediatric gliomas as neurodevelopmental disorders. *Glia* 64: 879-895.
2. Bonfield CM, Steinbok P (2015) Pediatric cerebellar astrocytoma: a review. *Childs Nerv Syst* 31: 1677-1685.
3. Crout TM, Parks LP, Majithia V (2016) Neuromyelitis Optica (Devic's Syndrome): an Appraisal. *Curr Rheumatol Rep* 18: 54.
4. Tenembaum S, Chitnis T, Nishikawa I, Collongues N, McKeon A, et al. (2016) Neuromyelitis optica spectrum disorders in children and adolescents. *Neurology* 87: S59-S66.
5. Kline CN, Joseph NM, Grenert JP, van Ziffle J, Talevich E, et al. (2017) Targeted next-generation sequencing of pediatric neuro-oncology patients improves diagnosis, identifies pathogenic germline mutations, and directs targeted therapy. *Neuro Oncol* 19: 699-709.
6. Wells EM, Packer RJ (2015) Pediatric brain tumors. *Continuum (Minneapolis)* 21: 373-396.
7. Kantorová E, Bittšanský M, Sivák Š, Baranovičová E, Hnilicová P, et al. (2017) Anaplastic astrocytoma mimicking progressive multifocal leucoencephalopathy: a case report and review of the overlapping syndromes. *BMC Cancer* 17: 424.
8. Preziosa P, Sangalli F, Esposito F, Moiola L, Martinelli V, et al. (2017) Clinical deterioration due to co-occurrence of multiple sclerosis and glioblastoma: report of two cases. *Neurol Sci* 38: 361-364.