Anaplastic Cerebellar Ependymoma in an Adult Female presenting with Tonsillar Herniation successfully treated with Chemotherapy: A Case Report

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Abstract

Introduction: Ependymomas are slow-growing neuroectodermal tumors that may arise from various parts of the central nervous system. Anaplastic ependymoma represents 3-5% of ependymomas, and it is rarely found in adults and the infratentorial area, particularly the cerebellum. This paper discusses the first reported case of an adult female with anaplastic cerebellar ependymoma who underwent surgery and was treated with chemotherapy for tonsillar herniation.

Case Presentation: This is a case of a 58-year-old Filipino female with a five-month history of dizziness, headache, nausea, and vomiting. Cranial computed tomography (CT) scan revealed the presence of hydrocephalus with enhancing lesions at the right cerebellum. The patient underwent ventriculoperitoneal shunting (VPS) with sub-total excision and biopsy of the right cerebellum. Histology and immunochemistry were consistent with a high-grade anaplastic ependymoma (WHO Grade III). Cerebrospinal fluid and spinal magnetic resonance imaging (MRI) were negative for tumors. The initial plan was to undergo limited field external beam radiation therapy to the cerebellum. However, the patient was lost to follow-up. Two months after surgery, she presented with similar symptoms. MRI revealed tonsillar herniation and interval progression of the mass compressing the fourth ventricle, pons, and medulla oblongata; thus, medical decompression urgent chemotherapy with cisplatin and etoposide were started. After four chemotherapy sessions, repeat cranial MRI revealed resolution of tonsillar herniation and interval regression of the mass.

Conclusion: This paper presented a rare case of anaplastic cerebellar ependymoma with tonsillar herniation, successfully treated with chemotherapy. Radiotherapy is the standard of care following surgical resection. Still, our case management showed that in a patient with tumor progression presenting with tonsillar herniation, alternative management is to give systemic chemotherapy instead of radiotherapy.

Keywords: anaplastic cerebellar ependymoma, chemotherapy, herniation

Introduction

Ependymomas in adults account for only 3% of all primary central nervous system tumors diagnosed each year in the United States.[1-2] These tumors are slow-growing neuroectodermal tumors that may arise from various parts of the central nervous system and are classified under WHO Grade I-III. The incidence and the location of the tumor vary by age. Ependymoma arising from the spinal cord is more common among adults (50-60%) but is rare in the pediatric age group (20%).[1,3] Conversely, infratentorial or cerebellar ependymoma incidence is less frequent in adults, and anaplastic cerebellar ependymoma represents 3-5% of ependymomas[1-4,5]. The 2004–2009 average annual age-adjusted incidence rate of adult ependymal tumors was 0.41/100,000.[4.] Locally, a retrospective study at the Philippine General Hospital from the year 2010 to 2015 documented only seven ependymoma cases. In this local study, none was found in the cerebellum, and none showed the presence of herniation.[6] In another retrospective study done in China from 2004 – 2015, eleven patients were documented to have intracranial anaplastic ependymoma. Among these patients, only three had anaplastic ependymoma of the cerebellum, one of whom was in the elderly age group.[7]

Ependymoma is a genetic disease like other cancers, and the molecular basis for the development and progression of this tumor remains controversial. Cytogenetic studies done in the past have identified that loss of 22q is the most common genomic imbalance. Other genomic imbalances in intracranial ependymomas include a gain of 1q and losses of 6p and 9. It is now well known that ependymomas in other areas of the CNS are marked by peculiar gene expression signatures that indicate deregulation of the developmental pathways involved in tumor growth and progression. Tumor progression and recurrence

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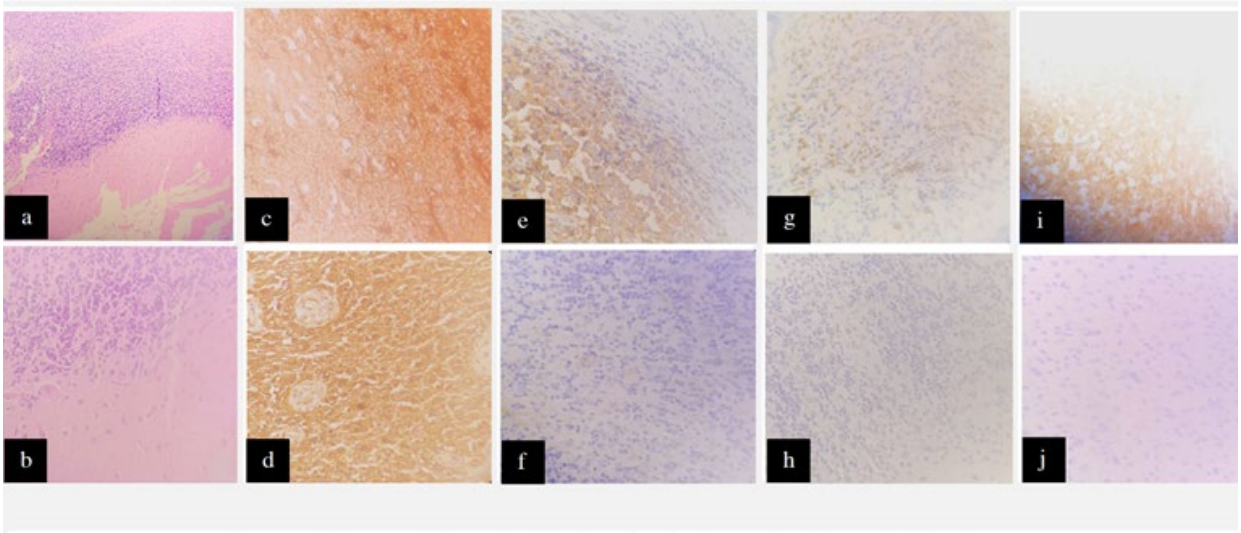

Figure 1. Immunohistochemical analysis of anaplastic cerebellar tissue

a, in low power filed (LPF); **b-j,** in high power field (HPF). **a, b** - Cerebellar cortical tissue in hematoxylin and eosin (H&E) stain showing moderate nuclear polymorphism with areas showing up to 14 mitosis / 10 high power field. **c, e, f, and i,** control slides for GFAP, EMA, p53 and IDH-1 respectively. **d.** GFAP positive cerebellar cortical tissue diffusely infiltrated by round fibrillary tumor cells. **f.** EMA positive cytoplasmic and dot-like pattern in few tumor cells. **h.** p53 positive in tumor cells. **j.** IDH-1 negative tumor cells.

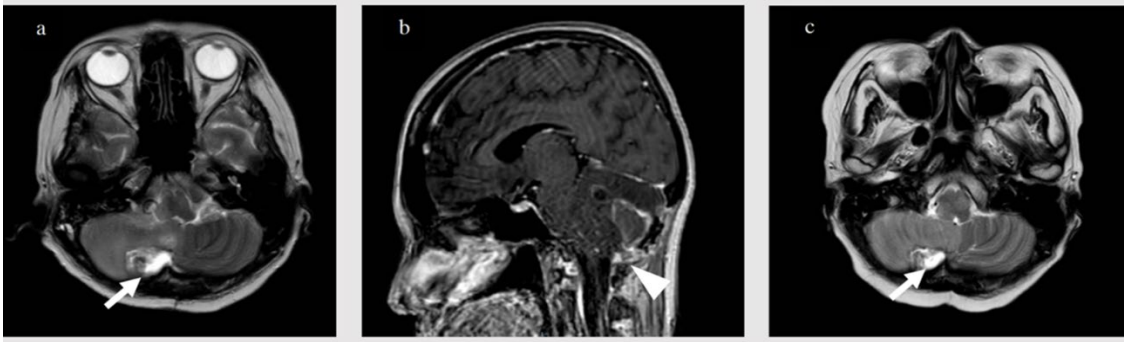

Figure 2. Contrast-enhanced cranial MRI.

Contrast-enhanced MRI showing areas of heterogenous enhancement seen in right cerebellar hemisphere (arrow) and right cerebellar peduncle over-all measuring 5.7 cm AP x 5.4 cm width x 5.3 cm height. (**a**: coronal view; **b**: sagittal view). This shows mass effect compressing; the 4th ventricle, pons, and medulla oblongata (arrow head). **Figure 2-c** shows interval regression of the said mass after 4 chemotherapy sessions (arrow) and showed partial response as per RANO criteria now measuring 2.8 cm x 2.5 cm x 2.3 cm.

are also likely due to the upregulation of Wnt signaling and down-regulation of the immune function-related genes. [21]

The current standard therapy for all anaplastic ependymoma is gross total resection (GTR) followed by limited adjuvant field external beam radiation therapy [1,13-14]. However, a common acute complication of patients undergoing radiotherapy for head and neck neoplasms is radiation-induced brain injury causing increased intracranial pressure.[1, 15] In this paper, we present a rare case of anaplastic cerebellar ependymoma in an elderly patient, presenting with tonsillar herniation and are managed with surgery and chemotherapy.

Case Presentation

This is a case of a 58-year-old Filipino female with a five-month history of dizziness, headache, nausea, and vomiting. The patient has no known comorbidities, is a non-smoker and non-alcoholic beverage drinker, and has no family history of malignancy or CNS tumors. A consult was done at a local private hospital, and she was diagnosed with vertigo. She was prescribed anti-vertigo medications which partially resolved her symptoms. In the interim, dizziness persisted; hence a plain cranial computed tomography (CT) scan revealed an infarct at the cerebellar area, and she was discharged after nine days. The patient only had minor improvement in her symptoms and still had a recurrence of dizziness, but no further consult was done. Two months after discharge, the patient had progressive weakness and dizziness and was bedridden for days. The patient underwent a cranial CT scan with IV contrast that showed the presence of hydrocephalus with an enhancing lesion at the right cerebellum. She then underwent ventriculoperitoneal

shunting (VPS) with near-gross total resection and the right cerebellar mass biopsy. Histopathology of the tumor showed cerebellar tissue diffusely infiltrated by round and fibrillary tumor cells positive for epithelial membrane antigen (EMA), glial fibrillary acidic protein (GFAP), and p53 and negative for isocitrate dehydrogenase (IDH-1) (*Figure 1*). The final histopathological report was consistent with a high-grade anaplastic ependymoma, World Health Organization (WHO) Grade III. The cerebrospinal fluid analysis and spinal magnetic resonance imaging (MRI) were negative for the tumor.

The initial plan was to undergo limited field external beam radiation therapy to the cerebellum, but the patient was lost to follow-up. Two months after the surgery, she presented with similar symptoms until she was seen with signs of increased intracranial pressure at the emergency room. In addition, there was noted bilateral horizontal nystagmus, dysmetria, ataxia, and poor coordination on physical examination. Initial cranial magnetic resonance imaging (MRI) revealed tonsillar herniation and interval progression of the mass at the cerebellar peduncle measuring 5.7 cm x 5.4 cm x 5.3 cm compressing the fourth ventricle, pons, and medulla oblongata (*Figure 2 - a, b*). Medical decompression with dexamethasone 10mg IV 5mg IV q6 and mannitol 100mg IV then 100mg IV pre-chemotherapy was started. Urgent chemotherapy was given every 28 days: cisplatin at 25 mg/m^2/day from days 1-3 and etoposide 100 mg/m^2/day from days 1-3 with granulocyte-colony stimulating factor (G-CSF) support on day 7. There were no treatment interruptions, and the patient tolerated all of the cycles well. Therefore, the further plan includes radiotherapy once with the resolution of herniation. The patient had no significant toxicity during chemotherapy: the major toxicity observed was grade 2 alopecia and grade 1 fatigue based on the Common Terminology Criteria for Adverse Events (CTCAE Version 5.0). Steroid doses were also tapered until eventually discontinued. After four cycles of chemotherapy, repeat cranial MRI revealed (1) interval resolution of tonsillar herniation (2) resolution of edema, and (3) regression of the mass measuring 2.8 cm x 2.5 cm x 2.3 (*Figure 2 - c*). The patient had a partial response to treatment based on the Response Assessment in Neuro-Oncology (RANO) criteria: 50% decrease in the sum of perpendicular diameters, no new lesions, freedom from steroids, and clinical improvement. The patient was also asymptomatic at this time.

Discussion

Ependymal tumors are derived from ependymal cells, a subtype of glial cells essential for CSF production. These cells line the cerebral ventricles and the spinal canal.[5,8] According to the 2016 WHO classification of CNS tumors, ependymal tumors are classified from Grade I-III.[9] Anaplastic ependymomas are classified under WHO grade III. These are commonly intracranial and comprise about 30% of cases in 0–19 years of age compared with only about 3–5% in adult age groups.[4,10] Ependymoma arising from the spinal cord is more common among adults (50-60%). Posterior fossa or cerebellar anaplastic ependymoma is more common in the pediatric population than the adult population representing only 3-5% of anaplastic ependymomas[1-4,5]. These tumors have a high proliferative rate and tend to infiltrate and spread to the surrounding brain tissue or the CSF, causing drop metastasis[1,11]. In the large cohort study using the USA National Cancer Database to study adult WHO grades II/III supratentorial and posterior fossa ependymoma patients treated between 1998 and 2011, they were able to describe 1,318 adult patients (18 years and older) with supratentorial and posterior fossa ependymoma, 263 (20.0%) had WHO grade III anaplastic ependymoma and among which, 60 (22.8%) had the tumor located in the posterior fossa and 203 (77.2%) at the supratentorial region (12). The overall percentage of patients with anaplastic ependymoma located at the posterior fossa in this study is 12.7%. The average age of occurrence for anaplastic ependymoma is 43 years of age; 52% were females with no comorbidities. The incidence of having anaplastic ependymoma in the supratentorial region is thrice as much as in the infratentorial region. Among these patients, 97 received near-gross total resection, 201 patients received radiotherapy, and only 54 received chemotherapy. The oldest patient diagnosed with anaplastic ependymoma was 54 years old in the same study. In comparison, our patient is a 58-year-old female without known comorbidities and underwent near-gross total resection but did not undergo radiotherapy since the patient was lost to follow-up and already presented with tonsillar herniation.[12]

Anaplastic cerebellar ependymoma is a life-threatening neoplasm mainly because it causes an increase in intracranial pressure due to the limited space and compact structure of the posterior fossa where it is located. Common symptoms of posterior fossa tumors are mainly related to the mass effect of the enlarging tumor and obstructive hydrocephalus. At the time of presentation, patients may experience nausea, vomiting, and dizziness, which were all present in our patient. In addition, some patients may present with cranial nerve neuropathies causing extraocular muscle disorders, which were not observed in our patient. VPS was used to relieve the elevated intracranial pressure due to the obstructing hydrocephalus.[13] However, despite the VPS, the patient still became symptomatic and experienced tonsillar herniation.

The current standard therapy for all anaplastic ependymoma is gross total resection (GTR), but this is difficult to achieve in the posterior fossa.[1] Since anaplastic ependymomas have a high propensity to invade surrounding structures, adjuvant limited field external beam radiation therapy is considered by most as the standard treatment.[1,13-14] However, in patients undergoing radiotherapy for head and neck neoplasms, radiation-induced brain injury causing increased intracranial pressure from brain edema is a common acute complication. Given the case of our patient where her MRI showed the presence of herniation, radiation therapy will likely progress and aggravate this.[15] Chemotherapy before radiotherapy can be an option in anaplastic ependymoma.[16-17] In a case report done in Italy, a 45-year-old female with recurrent supratentorial anaplastic ependymoma who

had four neurosurgical operations for the recurrent tumor, underwent combination chemotherapy using cisplatin and temozolomide given every 21 days showed interval reduction in tumor size and progressive clinical improvement after two cycles of chemotherapy, however the indication for chemotherapy was not due to herniation but due to recurrent mass but showed a beneficial effect in tumor size reduction. The patient had a stable lesion for the entire duration of treatment (10 cycles) but had progression of the disease after six weeks since the last chemotherapy session.[18] In a multicenter retrospective study done in three Italian institutions from 1993 to 2003, patients diagnosed with intracranial WHO grade II or III ependymoma and had prior surgery and radiotherapy for recurrent tumor showed better response rate in terms of tumor resolution using cisplatin-based chemotherapy compared to non-cisplatin based regimen but did not prolong the overall survival. The median overall survival with cisplatin-based chemotherapy in this study was 31 months from the start of chemotherapy.[19] Data on primary post-operative treatment using chemotherapy alone is relatively uncommon in adult patients with anaplastic ependymoma but is common in children younger than three years old to prevent radiation-induced effects on the nervous system and cognition. Post-operative chemotherapy in children delayed the need for radiotherapy and did not compromise the overall survival.[20] Surgical excision followed by radiotherapy with or without concurrent chemotherapy is the most common option in adult patients. In a retrospective study by Gramatzki and colleagues, they evaluated 17 patients with WHO grade II to III ependymoma who underwent surgical removal of the tumor (partial, subtotal, or gross total resection). Among these patients, only 2 had chemotherapy with concurrent radiotherapy. Survival outcomes vary substantially due to the limited number of patients. [17]

In the retrospective study done using the USA National Cancer Database to study adult WHO grades II/III supratentorial and posterior fossa ependymoma, it was found out that there was no effect in the overall survival in the cohort with anaplastic ependymoma, who received radiation therapy and no benefit documented in terms of overall survival in those receiving chemotherapy as part of the first course of treatment. However, it is useful in certain circumstances, such as in patients presenting with herniation. Furthermore, older age at diagnosis, high tumor grade, and large tumor size (≥ 4 cm) were associated with poor survival, and the median overall survival for anaplastic tumors was 49.7 months. The low prevalence of intracranial ependymoma in adults limits extensive studies; thus, treatment recommendations and options are based primarily on retrospective studies and pediatric protocols.[17]

Conclusion

In patients diagnosed with anaplastic ependymoma located in the cerebellum, the standard of care is still gross total resection followed by radiation therapy, but in cases where there is tumor progression and herniation, radiation therapy may be contraindicated. Alternative management is to give chemotherapy rather than radiation therapy, thus preventing further complications of herniation. Chemotherapy in patients with herniation is effective and is well tolerated.

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