Rare Case Report of Cerebral Ganglioneuroblastoma

Vaghela Manan P[1], Panchal Harsha P[2], Anand Asha S[2], Patel Apurva A[2], Parikh Sonia K[3], Shah Sandip A[3], Dadhania Jay[1], Shah Rushit[1]
Resident[1], Professor[2], Associate Professor[3]
Department of Medical and Pediatric Oncology
Corresponding Author: drharshapanchal@gmail.com

Summary

Ganglioneuroblastomas (GNBs) are rare embryonic neoplasm in the spectrum of neuroblastic tumours and 80% of cases occur in the first decade. We describe a 14-year-old boy with acute onset headaches and limb weakness. On imaging he was diagnosed of having intra-cranial mass. Patient underwent partial excision of tumor, followed by chemo-radiotherapy. This mass was pathologically confirmed as a primary intracranial ganglioneuroblastoma, a rare finding in the pediatric population. For cerebral ganglioneuroblastoma, the preferred regimen would seem to be neurosurgical removal, followed by chemoradiotherapy including temozolomide.

Keywords: Brain, Ganglioneuroblastoma, Neuroblastoma

Introduction

Ganglioneuroblastoma (GNB) represents a subgroup of neuroblastoma tumors with prominent, mature ganglion cell differentiation, usually located in the adrenal gland, posterior mediastinum, or retro peritoneum. Neuroblastomas are neural crest tumors composed of undifferentiated neuroblasts with stroma poorly represented. In the presence of ganglion cells and stroma-rich areas, they are designated as ganglioneuroblastoma.[1-3] Neuroblastomas are classified among the group of primitive neuroectodermal tumors (PNET), which also include medulloepithelioma and ependymoblastoma (containing ependymoblastic rosettes).[1] Some author also include medulloblastoma within the group of PNET's. More than 90% of all ganglioneuroblastomas are seen in children younger than 5 years old and it is rare that they appear in adults. These neoplasm arise wherever sympathetic tissue exists and may be seen in the neck, posterior mediastinum, adrenal gland, retro peritoneum, and pelvis.[4,5] Central nervous system neuroblastomas and GNB are uncommon. Signs and symptoms of cerebral neuroblastic tumors are related to the site of origin, and include seizures, disturbances of consciousness, increased intracranial pressure, and motor deficit.

Case Report

We report a case of 14-year-old child presented with gradually increasing headache since two months, nausea and vomiting since 15 days and left upper limb and lower limb weakness since five days. The previous history was otherwise negative. Physical examination showed a left upper limb weakness (power 2/5) and left lower limb weakness (power 3/5). MRI Brain showed 25 x 24 x 24 mm lesion, at left cerebellopontine angle with mass effect which is T1 hypointense, T2 hyperintense, homogenously enhancing with restricted diffusion with lepto meningeal enhancement. The patient underwent subtotal excision of space occupying lesion. Post operative MRI Brain with whole spine screening was suggestive of progression of disease in form of, altered signal intensity solid cystic lesion in left posterior cerebral region (77x15 mm), left temporal lobe region (47x33 mm) with post contrast enhancement and diffuse meningeal enhancement, suggestive of meningeal metastasis. CSF cytology was positive for malignant cells. Further work-up including CT scan of thorax and abdomen and bone scan showed no other tumor locations elsewhere. After surgery, the treatment was followed by chemoradiotherapy (40 Gy in 20 fractions with concomitant temozolomide (75 mg/m^2/day), post chemo radiotherapy MRI Brain with whole spine screening was suggestive of stable disease. It was followed by 6, monthly cycles of temozolomide (200 mg/m^2/day for 5 days, every 4 weeks). At present patient is receiving last cycle of adjuvant chemotherapy.

Histology

The histology of tumor was GNB. (Figure 1).The brain parenchyma was infiltrated by focally highly cellular proliferation of cells with round and hyperchromatic nuclei and a relatively small rim of cytoplasm, showing positive staining for

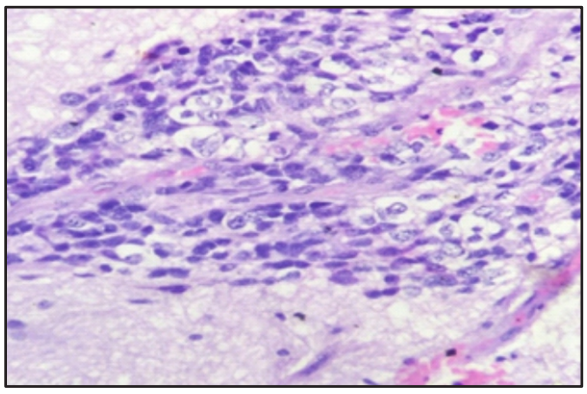

Figure 1: Histopathology of H & E stained slide of cerebral GNB

synaptophysin, NSE, CD-56. INI1 retained. In between these cells we observed several larger cells with neuronal features, often with irregular nuclei, sometimes showing a double nucleus. MAP2 was positive in ganglion cell. Ki-67 positivity was 25%.

Discussion

GNB is defined by the International Neuroblastoma Pathology Committee (INPC 1999)[3] and classified as a subgroup of neuroblastoma.[6] GNB is a mixed tumor including mature ganglion cells and malignant neuroblastoma simultaneously.[2,3] Degree of GNB differentiation is between high malignant neuroblastoma and benign ganglioneuroma.[7] However, it is difficult to draw a clear demarcation line based on morphology or gene expression differences.

The most common sites of origin of GNB are the adrenal medulla, extra-adrenal retroperitoneum, and posterior mediastinum. Less common sites are the neck and pelvis.[5] although rare, the GNB may also occur at the central nervous system, mainly involving the cerebral hemispheres. The location of intracranial GNB, including frontal, temporal, parietal, occipital, parietal-occipital, pineal, cerebellar, cerebellopontine region and ventricle, determine its clinical symptoms, such as seizures, visual impairment, hemianesthesia, unilateral sensory, motor disturbance, headache, and transient global amnesia.MRI often showed features of low-grade gliomas, including a space-occupying lesion with a well-defined margin. Hyper-signal on DWI with a low ADC value was detected, which prompted high tumor malignancy. Furthermore, Magnetic Resonance Spectroscopy analysis showed an increase of Cho/NAA.

GNB is composed of neuroblastoma cells, ganglion cells with different degrees of differentiation, nerve sheath, and glial fibers.[8, 9] the common characteristic of pathological findings is the highly infiltrated and proliferated cells with dense chromatin. Ganglion-like large cells usually present with double nucleus.[10] Immunohistochemical staining for S100, neurofilaments, chromogranin, NSE, CD34, and synaptophysin was positive in ganglion cells and nerve sheath cells.[11–16] S100, synaptophysin, neurofilaments were positive in neuroblastoma

Table 1: Cases of ganglioneuroblastoma reported in the literature

First author	Location	Metastasis	Surgery (complete/partial resection)	Radiotherapy	Chemotherapy	Survival
Raina et al. [22]	Spinal cord	None	Complete	-	Adriamycin, cyclphosphamide, vincristine, etoposide, ifosphamide, cisplatinum	>24 m
Sibilla et al. [23*]	Spinal cord	Local	-	-	-	>3 m
Tripathy et al. [24]	Spinal cord	None	Complete	-	-	>6 m
Feigin and Cohen [7]	Brain	Metaststic disease		-	-	0.5 m
Nakajima et al. (1982)	Brain		Complete	RT	Chemoth, unknown	>39m
Tanaka et al. (19980)[25]	Brain	None	Complete	50 Gy	-	>15 m
Nishihara et al. (2008)[26]	Brain	None	Complete	**	-	-
Sabatino et al. [27]	Brain	None	Complete	60 Gy local	Temozolomide	>18 m
M.H. Schipper et al.[29]	Brain	None	Complete	60 Gy local	Temozolomide	>14 m
M.H. Schipper et al.[29]	Brain	None	Partial	60 Gy local	Temozolomide	>12 m

(*) – Not received any form of therapy
(**)- Radiotherapy details not available

cells.[17,18] In our case, histopathology showed the positive staining of synaptophysin , NSE , CD-56. INI1 retained. MAP2 - positive in ganglion cell. Ki-67 was 25%.

GNB is further divided into 2 subtypes (undifferentiated and poorly differentiated types) [24] under electron microscope. The undifferentiated type consists of small round-to-oval cells with hyper chromatic nuclei.[19] the poorly differentiated type is composed of large round-to-oval spindle-shaped cells with pale staining nuclei.[19]

Complete resection is the optimal treatment for intrarcranial GNB. Partial resection or subtotal resection should be performed if the tumor extends into the cavernous sinus. Moreover favorable outcome will be obtained after fractionated radiotherapy and chemotherapy. It was reported that the longest asymptomatic period of the patients with intracranial GNB is 60 months following the above treatment.[20] although the rare occurrence of ganglioneuroblastoma makes prospective trials virtually impossible; patients treated with combinations therapy including chemoradiation using temozolomide have shown the longest survival.[21]

For literature review, pubmed and google scholar database was chosen. On literature review ten adult cases of ganglioneuroblastoma have been reported with in the central nervous system, of whom three in the spinal cord and seven in the brain. Details of these patients are described above in table. Out of these ten patients, two patients did not receive any form of therapy. Survival is improved with trimodality therapy inform of surgery followed by chemo-radiotherapy. Chemotherapy agents used include: adriamycin, cyclophophamide, vincristine, etoposide, ifosphamide, cisplatin, temozolamide. Our patient underwent subtotal excision, and chemoradiotherapy (40 Gy) with temozolomide, according to the Stupp schedule.[21] At present patient is receiving last cycle of adjuvant chemotherapy.

Table 1 shows cases of ganglioneuroblastoma reported in the literature. Recently immunotherapy as treatment for neuroblastomas was reported as being successful.[28] For ganglioneuroblastoma it is unknown, whether immunotherapy may be beneficial.

Conclusion

Cerebral GNB is rare presentation of GNB. For cerebral GNB, the preferred regimen would now seem to be neurosurgical removal, followed by chemoradiotherapy including temozolomide followed by adjuvant chemotherapy with temozolamide.

Abbreviation

GNB: Ganglio Neuro Blastoma, MRI: Magnetic Resonance Imaging, PNET: Primitive Neuro Ectodermal Tumor.

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