CASE REPORT

Glioblastoma with primitive neuronal pattern in a girl aged 3 months: a rare diagnosis at an unusual age

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SUMMARY

A girl aged 3 months presented with multiple seizures within 12 hours and was noted to have a palpable swelling over the right temporal region. MRI of the brain revealed a large right frontotemporal tumour, suggestive of supratentorial primitive neuroectodermal tumour. She underwent a stealth-guided craniotomy and debulking of the tumour. Histopathology and immunochemistry of the specimen, however, indicated a high-grade tumour with glioblastoma and neuroblastic components. She underwent adjuvant chemotherapy following the surgery and is well at 7-month follow-up. This case underscores the importance of considering the rare entity of glioblastoma with primitive neuronal pattern as a differential diagnosis in a young child.

BACKGROUND

Brain tumours with simultaneous glioblastoma and primitive neuroectodermal components are particularly unusual. The average age at diagnosis is middle age.^{1 2} We describe the occurrence of this pathology in a girl aged 3 months. This is the first case report in the current literature of such a tumour in an infant. The 2016 WHO Classification of Tumours of the Central Nervous System has recognised the rare entity of glioblastoma with primitive neuronal pattern,³ which was frequently addressed as glioblastoma with primitive neuroectodermal tumour (PNET) component in the previous literature. It consists of diffuse astrocytoma of any grade with well-demarcated areas of primitive cells displaying neuronal differentiation. This diagnosis is poorly characterised and poses diagnostic challenge due to the concurrence of two distinct elements with different clinical, radiological and histopathological features. Glioblastoma is the most common malignant primary brain tumours in adults. On the other hand, supratentorial PNETs, composed of undifferentiated primitive neuroectodermal cells, are primarily found in the paediatric population. However, the term has been removed from the new diagnostic lexicon published in May 2016.³ Small foci of primitive-appearing cells are common even in classic glioblastomas; hence, morphological results should be combined with immunohistochemical findings to confirm the diagnosis of glioblastoma with primitive neuronal component.⁴ With the release of the new WHO classification of central nervous system tumours, this case also contributes to the current literature of this rare

diagnosis to assist with recommendation of treatment strategies.

CASE PRESENTATION

A baby girl aged 3 months presented with six episodes of seizures over a period of 12 hours. Each episode lasted for 15–30 s and settled spontaneously. They were associated with bilateral eye deviation to the left, vomiting, apnoeic episodes and lip cyanosis. The child was fully awake between each seizure. She was born at 38 weeks via normal vaginal delivery. The pregnancy and delivery were uncomplicated. In particular, routine obstetric screening ultrasounds performed at 13 and 20 weeks of gestation did not demonstrate any abnormalities. Her head circumference was 35 cm at birth (85th centile). She was fully breastfed and up-to-date with her immunisations. The child had known anisocoria which was awaiting investigation at the time of presentation.

On examination, her vital signs were within normal ranges and her temperature was 36.4° C. Her Paediatric Glasgow Coma Scale was 14 (opening eyes to verbal stimuli). The head circumference was 44.5 cm (well above 97th centile). The anterior fontanelle was soft and pulsatile on palpation. An abnormal pulsatile, firm swelling was seen over the right temporal area, measuring 3×4 cm. The swelling crossed suture lines and its bony margins were palpable. The child's mother reported that the swelling had been present since the child was 3 weeks old. The right pupil was noted to be 3 mm in size and the left pupil was 2 mm. Both were reactive to light. There was no ophthalmoplegia and she was moving all four limbs with normal tone. Cardiovascular, respiratory and abdominal examinations were otherwise unremarkable.

INVESTIGATIONS

Full blood examination, urea, electrolytes and C reactive protein were within normal ranges. MRI of the brain revealed an 8.5×7.0×8.5 cm mixed solid and cystic lesion in the right frontotemporal region which expanded into the suprasellar and prepon-tine cisterns (figure 1). It was associated with 15 mm of midline shift to the left, effacement of the right lateral ventricle, dilation of the left lateral ventricle, ipsilateral uncal herniation and remodeling of overlying calvarium. Heterogenous enhancement was particularly noted on the linings of the cystic areas within the tumour. Most of the solid

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Figure 1 Preoperative T1-weighted MRI brain images—precontrast axial (A) and postcontrast axial (B) showed a mixed solid and cystic lesion in the right frontotemporal region. Heterogenous enhancement noted on the cystic walls. Postcontrast coronal (C). Postcontrast sagittal (D). The absence of restriction diffusion (E) and reduced ADC values (F) noted within the tumour.

tumour demonstrated reduced apparent diffusion coefficient values but enhanced diffusely. Spectroscopy revealed low *N*-acetylaspartate, increased choline and high lactate. There was no evidence of leptomeningeal, ependymal or spinal enhancement.

DIFFERENTIAL DIAGNOSIS

Differential diagnoses included supratentorial PNET and atypical teratoid/rhabdoid tumour.

TREATMENT

The child was initially treated with levetiracetam 140 mg daily and dexamethasone 4 mg twice a day. She underwent a stealth-guided craniotomy and excision of the tumour on day 4 of admission. Straw-coloured fluid was aspirated from the large cystic component. The rubbery solid component was debulked,

leaving residual tumour medially around the right middle cerebral artery adjacent to the third ventricle.

OUTCOME AND FOLLOW-UP

Histopathological examination of multiple varied specimens (figure 2) demonstrated a high-grade cellular tumour with predominantly sheets of large cells with ample eosinophilic cytoplasm, including gemistocytic astrocytes, and moderate to severe nuclear pleomorphism. Scattered foci of pseudopalisading necrosis, prominent vascular proliferation and atypical mitotic figures were seen. Hypercellular regions with increased cellular density which appeared well demarcated from large cells were represented by smaller tumour cells with scant cytoplasm and high nuclear to cytoplasmic ratio. Some cells displayed medulloblastoma-like cytological features. Perivascular pseudorosette formation was seen, but Homer-Wright rosettes were

Figure 2 Microscopic examination depicted. (A) Interface of atypical gemistocytic astrocytic cells and dense, compactly arranged primitive neuroblastic cells with scant cytoplasm on H&E stain. (B) Strong vimentin positivity in the glial component. (C) Perivascular pseudorosette demonstrated in the primitive neuroectodermal tumour (PNET) component on H&E stain. (D) Positive GFAP staining in the glial component and negative GFAP staining in the PNET component. (E) Some cells with CD99 staining. (F) Primitive neuronal cells with strong synaptophysin positivity.

not obvious. The astrocytic components showed strong, diffuse staining of tumour cells for glial fibrillary acidic protein (GFAP), S100 and vimentin but lacked reactivity for synaptophysin. In contrast, the primitive neuronal areas were positive for synaptophysin and CD99 but negative for GFAP. Ki-67 immunostain showed a high proliferative index (20%) with increased staining of tumour cells in densely cellular regions with decreased staining elsewhere. INI-1 stain was preserved, excluding an atypical rhabdoid/teratoid tumour, and Neu-N was negative. IDH1 R132H immunohistochemistry was negative. IDH sequence

analysis was not performed. The tissue from cystic regions surprisingly did not display any tumour involvement. These findings were consistent with a high-grade malignant glioneuronal tumour with a heterogenous morphological pattern and an immunohistochemical profile indicative of divergent differentiation with predominantly glioblastoma features and areas closely resembling supratentorial PNET.

Postoperatively, her anisocoria resolved and she recovered well without any neurological deficits. She was discharged home and subsequently started on adjuvant chemotherapy. Sixteen

Figure 3 Residual tumour noted at the medial portion of the right frontal lobe on postoperative postcontrast T1-weighted MRI images—axial (A) and coronal (B).

cycles of 3-weekly carboplatin-based chemotherapy were planned. At each session, the child was given intravenous cyclophosphamide 1200 mg/m², etoposide 100 mg/m², carboplatin 534 mg/m², subcutaneous filgrastim 5 µg/kg, mesna and ondansetron. She required admission 2 months later with further seizures. The dose of levetiracetam was increased and clonazepam was added for seizure management. An early postoperative MRI brain and spine demonstrated stable residual tumour (figure 3) and no evidence of spinal seeding. At 7-month follow-up, she had completed six cycles of chemotherapy. She is doing well with no neurological deficits and is currently awaiting the seventh cycle of chemotherapy. A late repeat MRI brain shows reduction in residual enhancing tumour mass.

DISCUSSION

The largest case series of glioblastoma with PNET-like components was described by Perry *et al*¹ in 2008. The series included patients from 21 to 80 years old, with the exception of two paediatric patients. There are only six paediatric cases of glioblastoma with PNET components reported in the current literature (age range 7–17 years).^{1 5–7} To the best of our knowledge, the patient in our case is the youngest patient ever diagnosed with glioblastoma with primitive neuronal pattern. The presence of anisocoria at birth and noticeable early swelling over the location of the tumour, together with the absence of abnormalities on the 20-week obstetric ultrasound, strongly suggests the presence of the tumour during the first month of life and possibly even during late gestation. However, the mother did not have any further obstetric imaging beyond 20 weeks of gestation as per routine antenatal care schedule.

Glioblastoma and PNET are typically considered as two separate entities with different biological behaviours and treatment responses. Several theories have been proposed to explain the development of glioblastoma with primitive neuronal pattern. These include (1) development of differentiated glial tumour from pre-existing neuronal cells, (2) neuronal metaplasia phenomenon or de-differentiation of the astrocytic component resulting in neuronal cells, (3) collision tumour with two distinct clonal expansions⁸ and (4) development of both components from common stem cells.⁴ Evidence from the largest case series by Perry *et al* supports the origin of the primitive neuronal component from pre-existing glioblastoma as the median age of diagnosis in the case series is 54 years, unlike the average age of diagnosis for PNET. Evidently, our case report contradicts this theory. Pathogenesis of this particular tumour remains controversial at this stage due to the limited number of case reports and case series in the current literature.

The use of immunohistochemistry is important in confirming the diagnosis of glioblastoma with primitive neuronal pattern. Astrocytic cells usually show diffuse immunoreactivity for GFAP and vimentin but negative for synaptophysin, chromogranin and neuron-specific enolase (NSE). On the contrary, cells of neuroectodermal lineage are typically highlighted by immunoreactivity for synaptophysin, NSE, Neu-N and the absence of GFAP and vimentin immunoreactivity.^{2 9} In our case, the neuroblastic components represented by smaller tumour cells of higher cellular density demonstrate positive reactivity for synaptophysin and negative for GFAP, vimentin and Neu-N. In fact, Neu-N reactivity was only seen in 24% of the cases in the series by Perry.¹

Glioblastoma, being the most common malignant primary brain tumours in adults, is usually managed with surgical resection, radiotherapy and concomitant chemotherapy using alkylating agents such as temozolomide as per the Stupp protocol.¹⁰

Similarly, supratentorial PNETs are aggressive tumours with poor prognosis. Diagnosis of PNET requires further evaluation of the whole craniospinal axis to exclude tumour dissemination. Surgical resection is the first-line treatment, followed by craniospinal irradiation if the child is >3 years of age, with or without adjuvant platinum-based chemotherapy. Glioblastoma with primitive neuronal pattern has a similar poor median survival time to standard glioblastomas. It has been reported as 9.1 months in a large case series.¹ Metastatic rate has been described as up to 40% of cases, resembling the high dissemination rate of supratentorial PNETs and medulloblastomas. It is essential to recognise the primitive neuronal component within glioblastoma due to high risks of craniospinal dissemination and possible better response to platinum-based chemotherapy compared with alkylating agents. In our case, radiotherapy was not used and the child underwent adjuvant chemotherapy including the use of platinum-based antineoplastic agents. It is interesting to note that three patients in Perry's series initially failed a trial of radiotherapy and temozolomide but subsequently showed signs of therapeutic response after being switched to platinum-based chemotherapy. There is insufficient information in the literature at this stage to provide a conclusive treatment regimen for this pathology.

In summary, we present an unusual case of glioblastoma with primitive neuronal pattern in a girl aged 3 months. Histopathology and immunohistochemistry testing confirms a high-grade malignant glioneuronal tumour with divergent differentiation (WHO Grade IV). The recognition of this specific neurological entity by the new WHO classification of central nervous system tumours is an essential step towards facilitating emerging diagnostic tools in neuropathology and tumour management strategies. This case highlights the possible benefits of using adjuvant platinum-based chemotherapy agents such as carboplatin. Further research needs to be undertaken to evaluate the therapeutic response of this rare tumour to different chemotherapy agents.

Learning points

- It is important to consider the rare entity of glioblastoma with primitive neuronal pattern as a differential diagnosis in a young child, despite the average age of diagnosis around middle age based on the previous literature.
- Morphological results should be combined with immunohistochemical findings to confirm the diagnosis of glioblastoma with primitive neuronal component.
- Adjuvant platinum-based chemotherapy agents such as carboplatin may be more beneficial compared with alkylating agents due to high risks of craniospinal dissemination, resembling that of typical primitive neuroectodermal tumours.

Contributors CHT was responsible for the literature review and writing of the article. CX performed the surgery. TBP and CX were responsible for correction of the article and supervision.

Competing interests None declared.

Patient consent Obtained.

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