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Brain Pathology

CASE IMAGE

Under Your Microscope

Developmental delay and progressive seizures in 2-month-old child with diffuse MRI abnormalities

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1 | CLINICAL HISTORY

A term-born boy presented at age 2 months with the first episode of focal seizure, involving the left leg, and concern from a few weeks of age regarding delayed development. There was antenatal polyhydramnios without accompanying foetal abnormalities. He had never fixed, followed or cried. He was the first child of non-consanguineous parents with no relevant family history. Examination revealed weight <0.4th centile, length 9th centile, relative macrocephaly (50th centile), generalised hypertonia and absent oculocephalic reflexes with spared pupillary responses. He could suck but not grimace to stimuli. Hypertelorism and mild micrognathia were noted.

MRI with contrast showed disseminated, bilateral white matter changes with frontal sparing (Figure 1, Panel A), leptomeningeal and brain stem enhancement. Post-contrast enhancement was prominent in areas, including the optic chiasm, mammillary bodies and tectum (Figure 1, Panel B). There were no intramedullary lesions, although there was enhancement along the surface of the conus medullaris and the cauda equina. Cerebral aqueduct narrowing with lateral and third ventricle hydrocephalus was present. Electroencephalogram (EEG) showed a diffusely slowed background, with runs of seizure activity.

BOX 1 Slide scan

Access the whole slide scan at http://image.upmc.edu:8080/NeuroPathology/BPA/BPA-20-11-288/view.apml.

Craniotomy, brain biopsy and third ventriculostomy were performed. Brain biopsy was small, taken from the tuber cinereum. The biopsy showed glial tissue and Rosenthal-like granular intracytoplasmic deposits in the cell bodies, which raised a broad list of differential diagnoses. However, the biopsy material was limited and in the context of the clinical picture, a low-grade glioma remained a possible diagnosis.

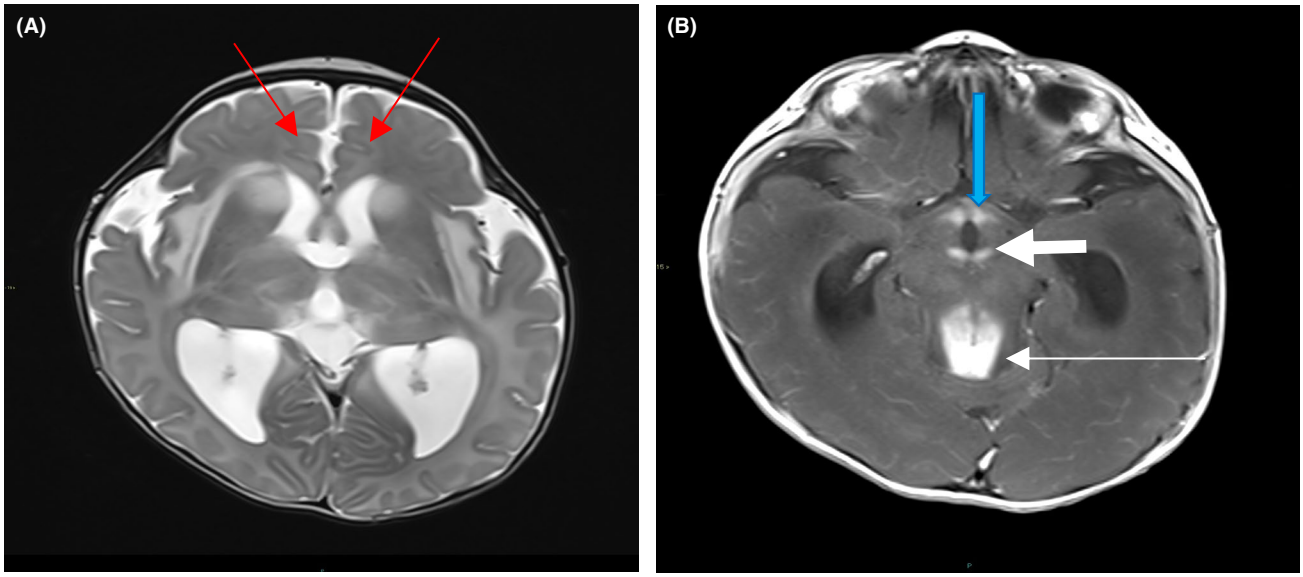

FIGURE 1 MRI features (Panels A and B): Diffuse, elevated T2 signal was seen but with frontal lobe sparing (red arrows) (A). Post-contrast imaging demonstrates prominent enhancement of the tectum (thin arrow), mammillary bodies (thick arrow) and optic chiasm (blue arrow) (B)

No *BRAF* mutation in exon 15 or *KIAA1549:BRAF* fusion transcript was detected. Re-biopsy was considered however not performed as there was a high risk of morbidity including damage to visual pathways.

Our patient was commenced on vincristine and carboplatin, which is standard first-line chemotherapy for low-grade glioma. He had tolerable chemotherapy side effects including culture-positive febrile neutropenia treated with intravenous antibiotics.

The patient experienced recurrent seizures over 8 wk manifested by left eye deviation and tonic upper limb posturing, worsening white matter changes and hydrocephalus, requiring a ventriculoperitoneal shunt. Subsequent EEGs demonstrated frequent sustained seizure activity from different hemispheric foci. Nasogastric feeding was commenced as a result of feed intolerance and vomiting. He deteriorated further with status epilepticus, requiring anticonvulsants, intubation and ventilation. Following

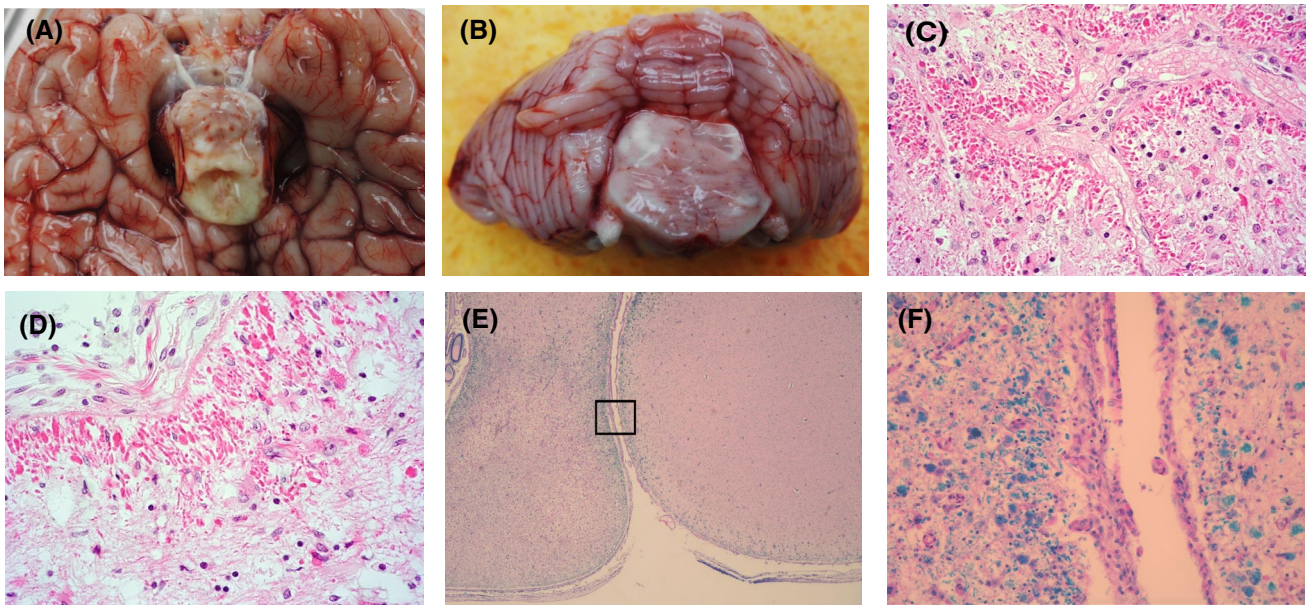

FIGURE 2 Macroscopic features (Panels A and B): The brain stem was pale and atrophic (A). A cut-section appeared yellow and granular with areas of cystic degeneration (B). Microscopic features (Panels C–F): Medullary sections showed perivascular Rosenthal fibre (RF) deposition, 20× magnification, with occasional glial cells with eosinophilic granules. (D) Subpial aggregation of RF, Medulla, 40× magnification. (E) LFB-PAS-stained section from the right parietal lobe demonstrated the distribution of Rosenthal fibres, stained blue, 20× magnification. (F) LFB-PAS-stained section from within the boxed area in Panel G, 200× magnification. Subpial aggregation of Rosenthal fibres, stained blue

extensive discussion with the team and the family, ventilatory support was withdrawn and the patient expired.

At autopsy, the brain showed mild cortical atrophy and dilated lateral ventricles with periventricular leukomalacia. The third ventricle was dilated and the aqueduct narrowed. Diffuse subcortical white matter change was seen in the parietal and temporal regions of the cerebrum, hypothalamic-chiasmatic region, basal ganglia, thalamus and sub-insular regions, with focal cystic degeneration. The cerebellum and brain stem were pale and appeared yellow, granular and cavitary (Figure 2, Panels A,B). Brain weight was 749 g (Box 1).

Perivascular Rosenthal fibres were seen, together with prominent subpial Rosenthal fibres, occasional glial cells with eosinophilic granules (Figure 2, Panel C [20× magnification], Panel D [40× magnification]). Subependymal regions and subpial areas also contained astrocytic cells with granular eosinophilic inclusions (figures not shown). Representative sections of the supratentorial pathology, stained with Luxol fast blue combined with periodic acid-Schiff (LFB-PAS), show characteristic blue staining of Rosenthal fibres (Right parietal lobe, Figure 2, Panels E,F).

2 | FINAL DIAGNOSIS

Neonatal Alexander disease.

3 | DISCUSSION

The clinical presentation, atypical imaging and biopsy findings caused diagnostic uncertainty, leading to a decision to treat as low-grade glioma pending definitive diagnosis. Genetic testing, available post-mortem, demonstrated a *GFAP* pathogenic germline variant (c.716G>T p.(Arg239Leu)). Characteristic pathological features at autopsy included Rosenthal fibres in astrocyte cell bodies. Parental testing in his asymptomatic mother showed maternal somatic mosaicism for this variant, with potential implications for maternal health and future pregnancies. Therefore, the autopsy findings and germline *GFAP* sequencing sent prior to death confirmed Alexander disease.

Alexander disease is an autosomal-dominant leukodystrophy caused by a mutation in the *GFAP* gene, which leads to gain of function and accumulation of abnormal protein that impairs astrocyte function [1]. Typical clinical features of neonatal Alexander disease are hydrocephalus, because of cerebral aqueduct stenosis, and persistent seizures as seen in our case [2]. The mutation is common de novo [1] and to our knowledge, maternal somatic mosaicism has not been previously reported.

The specific finding of Rosenthal-like granular intracytoplasmic deposits in the cell bodies from the biopsy raised the possibility of Alexander disease. Rosenthal fibres can be found in low-grade glial tumours, reactive gliosis, focal cortical dysplasia, fucosidosis, giant axonal neuropathy and Alexander disease. The presence of Rosenthal-like material in astrocyte cell bodies (as well as the more usual cell processes) is typical of Alexander disease [3].

The atypical radiological findings led to the consideration of neoplasia or a metabolic disorder. The rapidly progressive imaging changes, associated contrast enhancement and lack of frontal involvement were more suggestive of malignancy. The bilateral symmetrical involvement and age of onset were however against a diffuse neoplastic process and more consistent with a metabolic disorder.

Clinicians and pathologists need to consider Alexander disease in cases where bilateral widespread white matter changes are observed in association with Rosenthal fibres. In addition, the presence of Rosenthal-like granular glial inclusions in biopsies merits consideration of Alexander disease, even if characteristic Rosenthal fibres are absent. Diffuse leptomeningeal enhancement and lack of frontal leukoencephalopathy were atypical for Alexander disease and raised concern for a disseminated malignancy. Suggestive features for Alexander disease in this case were contrast enhancement in the brainstem, optic chiasm and meninges and especially Rosenthal fibres and Rosenthal-like inclusions in astrocyte cell bodies. Early use of genetic testing is recommended for diagnostic certainty, to guide patient management and parental counselling.

KEYWORDS:
histopathology, macrocephaly, neonatal Alexander disease, neonate, seizure

CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Marion K Mateos drafted and revised the manuscript, with input from all authors. Nikhil Birdi and Dipayan Mitra generated the radiology case images and commentary. Anna P. Basu provided neurology input. Michael Wright provided genetic expertise regarding the germline variant. Abhijit Joshi, Srinivas Annavarapu and Thomas S. Jacques provided pathology input and review. Abhijit Joshi and Srinivas Annavarapu generated the pathology case images. Simon Bailey provided expert clinical oversight. All authors approved the final manuscript.

DATA AVAILABILITY STATEMENT

Details for the germline *GFAP* pathogenic variant are included in the text.

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