Acta Neuropathologica (2019) 138:335–337
https://doi.org/10.1007/s00401-019-02027-7

CORRESPONDENCE

ALK-positive histiocytosis with *KIF5B-ALK* fusion in the central nervous system

Calixto-Hope G. Lucas[1] · Ahmed Gilani[2] · David A. Solomon[1] · Xiayuan Liang[2] · Ossama M. Maher[3] · Gabriel Chamyan[4] · Bette K. Kleinschmidt-Demasters[2] · Arie Perry[1]

Received: 26 April 2019 / Revised: 7 May 2019 / Accepted: 7 May 2019 / Published online: 22 May 2019

Keywords Histiocytic · ALK-positive histiocytosis · *KIF5B-ALK* fusion · Central nervous system

Histiocytic disorders are uncommon and often affect multiple organ systems. They pose diagnostic challenges because of their rarity and the fact that the nosology of these lesions is still being decided. ALK-positive histiocytosis is one of the newest subtypes and was originally described about 10 years ago, wherein there was a predilection for neonates and infants with multi-organ involvement [1]. Since then, ten additional cases have been reported, with only one having exclusive intracranial disease, along with involvement of the cavernous sinus [2, 3]. Here, we report two additional cases with exclusive involvement of the central nervous system.

Case 1 is a 7-year-old girl who presented with a 1-month history of headaches and vomiting. Magnetic resonance imaging (MRI) showed an infiltrating 3 cm mass in the cerebellar vermis. The mass was associated with diffusion restriction and was radiologically suspicious for medulloblastoma (Fig. 1a). She underwent gross total resection followed by observation with MRI every 3 months. Postoperative whole-body PET–CT scan showed no evidence of systemic disease. At 1-year postoperative follow-up, there is no evidence of recurrence on neuroimaging. Her only neurologic deficit is a minimal slurring of speech and difficulty with phonation.

Case 2 is a 10-year-old girl who presented with medically refractory seizures and was found to have a homogenously enhancing 1.4 cm mass in the right pericentral cortical region on head MRI (Fig. 1g). She underwent focal corticectomy followed by observation. Postoperatively, she has been doing well and has only had one reported seizure. She has not had a recurrent seizure while on antiepileptic therapy. At 6-month postoperative follow-up, there is no evidence of recurrence on neuroimaging. She has no remarkable findings on physical and neurological exam.

Consistent with prior reported cases, microscopic examination in both cases showed sheet-like aggregates of large epithelioid cells with irregularly folded nuclei and fine chromatin, foamy cells, Touton-like giant cells, and focal emperipolesis (Fig. 1b–e, h). Immunohistochemical workup in both cases showed ALK expression (Fig. 1f, i), Factor XIIIa, CD68 (Fig. 1j), and CD163 (Fig. 1k) positivity, patchy staining for S-100 protein, and lack of CD1a, BRAF V600E, or GFAP reactivity, although the latter highlighted adjacent and entrapped brain parenchyma with reactive astrocytosis (Fig. 1l). The histopathology observed in these cases of ALK-positive histiocytosis show overlapping features with those of Erdheim–Chester disease (ECD), juvenile xanthogranuloma (JXG), Rosai–Dorfman disease (RDD), and Langerhans cell histiocytosis (LCH). In particular, foamy cells, Touton-like giant cells, variable S-100 staining, and the presence of Factor XIIIa expression suggests the possibility of JXG or ECD [4]. Emperipolesis can be seen in RDD and folded or grooved nuclei are present in LCH. A CD1a immunostain can be used to further rule out LCH. Rarely, ALK-positive histiocytosis can also be confused with astrocytic lesions, particularly at intraoperative consultation

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00401-019-02027-7) contains supplementary material, which is available to authorized users.

✉ Arie Perry
arie.perry@ucsf.edu

[1] Division of Neuropathology, Department of Pathology, University of California, San Francisco, 505 Parnassus Ave, Room M-551, San Francisco 94143, CA, USA

[2] Department of Pathology, University of Colorado, Children's Hospital Colorado, Aurora, CO, USA

[3] Division of Pediatric Neuro-Oncology, Nicklaus Children's Hospital, Miami, FL, USA

[4] Department of Pathology, Nicklaus Children's Hospital, Miami, FL, USA

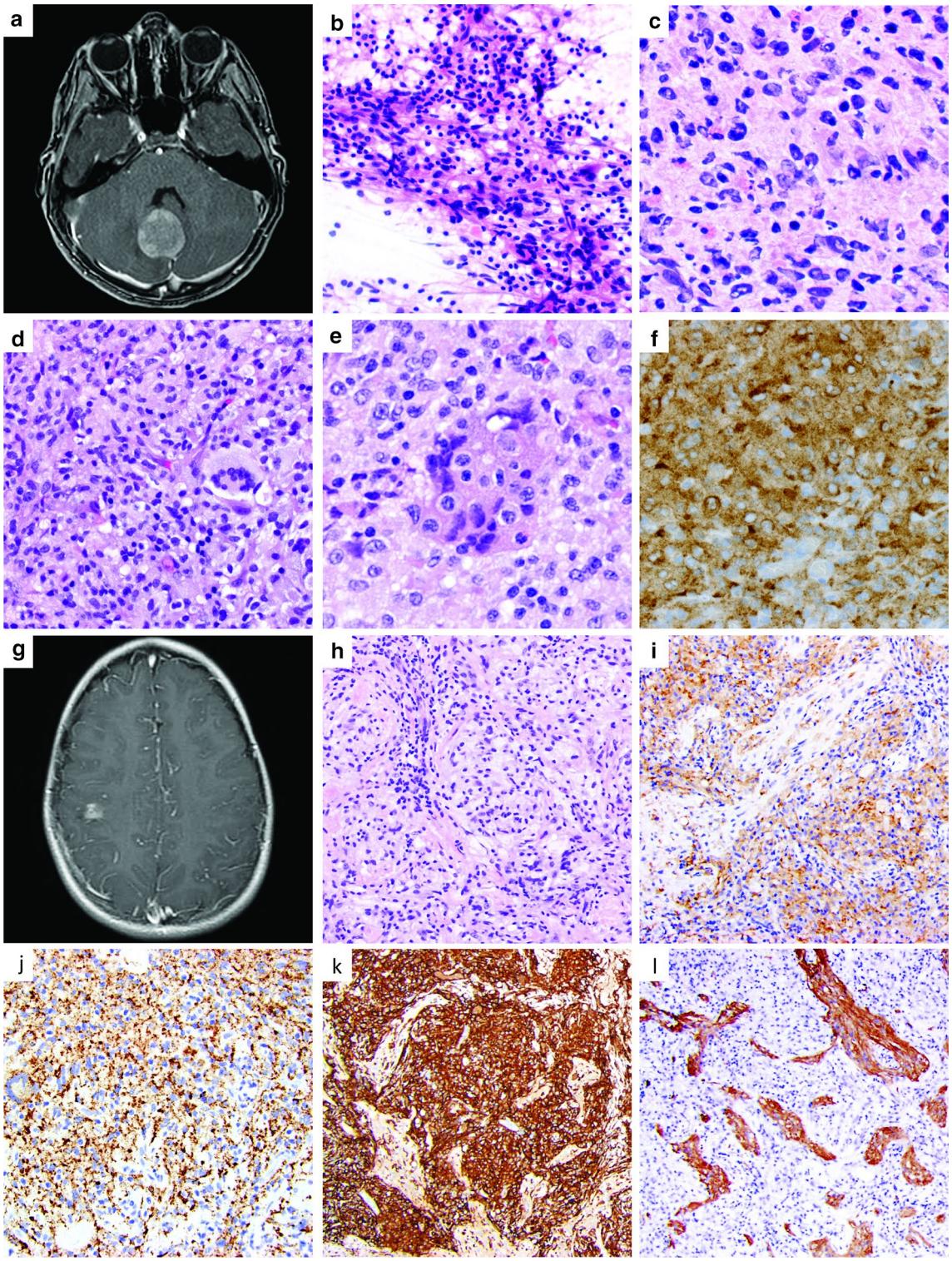

Fig. 1 Case 1, 7-year-old girl with a 3 cm enhancing cerebellar mass seen on MRI (**a**). Intraoperative smear showed multinucleation, pleomorphism and tapering eosinophilic cytoplasm which was initially confused with a glial neoplasm (**b**). Frozen section (**c**) and permanent sections (**d**–**f**) showed additional histologic features including Touton-like giant cells (**d**), nuclear grooves and emperipolesis (**e**), and ALK positivity (**f**). Case 2, 10-year-old girl with an enhancing 1.4 cm right-sided cortical mass seen on MRI (**g**). Histopathologic workup revealed a histiocytic lesion (**h**) with ALK positivity (**i**), CD68 positivity (**j**), CD163 positivity (**k**), and entrapped GFAP-positive gliotic brain (**l**)

where the presence of pleomorphic nuclei, multinucleation and tapering eosinophilic cytoplasm can resemble the histologic appearance of a pleomorphic xanthoastrocytoma (Fig. 1b).

Targeted next-generation sequencing identified in-frame *KIF5B-ALK* gene fusions in both cases. Both cases harbored fusions linking exons 1–24 of *KIF5B* to exons 20–29 of *ALK* [Supplementary Table 1 and Supplementary Figure 1 (Online Resource 1)], identical to the five systemic cases of ALK-positive histiocytosis described by Chang et al. [2]. In case 1, fusion testing was performed using the Archer FusionPlex Solid Tumor next-generation RNA sequencing assay targeting 53 genes. In case 2, targeted capture-based next-generation DNA sequencing was performed using the UCSF500 Cancer Panel as previously described [5]. No additional pathogenic mutations, amplifications, deletions, or fusions were identified involving any other targeted genes, including *BRAF, MAP2K1, KRAS, NRAS,* and *PIK3CA*.

Some histiocytic disorders can show specific genetic signatures. *BRAF* V600E mutation is the most common in both LCH and ECD and this is detectable using immunohistochemistry. Other MAPK pathway alterations are often found in those that are negative for BRAF V600E mutant protein. *ALK* gene fusions have been identified in a subset of histiocytic neoplasms [6, 7] including *KIF5B-ALK* in a case of ALK-positive histiocytosis. In the recently published series by Chang et al., five samples showed *KIF5B-ALK* gene fusion, with identical fusion breakpoints to the two localized central nervous system cases reported here [2]. Of note, *ALK* gene fusions are known to be present in a spectrum of other human tumors including lung adenocarcinomas and inflammatory myofibroblastic tumors and often correlate with sensitivity to small molecule kinase inhibitors such as crizotinib [8]. The prior report of an ALK-positive histiocytosis case responding to crizotinib [2] illustrates the utility of targeted therapy in the treatment of this disease entity. So far, in our two cases, this has not been necessary because both underwent gross total resection and have not shown any evidence of recurrence to date.

These cases, along with the recently published series by Chang et al., extend the clinical and histomorphologic spectrum of ALK-positive histiocytosis to include localized central nervous system involvement and a broader age range than previously appreciated [1]. These cases also underscore the importance of an integrated histologic and genetic approach for the diagnosis and treatment of challenging histiocytic central nervous system lesions.

Acknowledgements D.A.S is supported by NIH Director's Early Independence Award (DP5 OD021403). We thank the staff of the UCSF Clinical Cancer Genomics Laboratory for assistance with genetic profiling.

References

1. Chan JK, Lamant L, Algar E et al (2008) ALK+ histiocytosis: a novel type of systemic histiocytic proliferative disorder of early infancy. Blood 112(7):2965–2968. https://doi.org/10.1182/blood-2008-03-147017
2. Chang KTE, Tay AZE, Kuick CH et al (2018) ALK-positive histiocytosis: an expanded clinicopathologic spectrum and frequent presence of KIF5B-ALK fusion. Mod Pathol 32(5):598–608. https://doi.org/10.1038/s41379-018-0168-6
3. Huang H, Gheorghe G, North PE, Suchi M (2018) Expanding the phenotype of ALK-positive histiocytosis: a report of 2 cases. Pediatr Dev Pathol 21(5):449–455. https://doi.org/10.1177/1093526617740784
4. Louis DN, Ohgaki H, Wiestler OD et al (2016) WHO Classification of Tumours of the Central Nervous System (revised 4th edition). International Agency for Research on Cancer (IARC), Lyon, France
5. Kline CN, Joseph NM, Grenert JP et al (2017) Targeted next-generation sequencing of pediatric neuro-oncology patients improves diagnosis, identifies pathogenic germline mutations, and directs targeted therapy. Neuro-oncology 19(5):699–709. https://doi.org/10.1093/neuonc/now254
6. Diamond EL, Durham BH, Haroche J et al (2016) Diverse and targetable kinase alterations drive histiocytic neoplasms. Cancer Discov 6(2):154–165. https://doi.org/10.1158/2159-8290.CD-15-0913
7. Estrada-veras JI, O'brien KJ, Boyd LC et al (2017) The clinical spectrum of Erdheim–Chester disease: an observational cohort study. Blood Adv 1(6):357–366. https://doi.org/10.1182/bloodadvances.2016001784
8. Yoshihara K, Wang Q, Torres-garcia W et al (2015) The landscape and therapeutic relevance of cancer-associated transcript fusions. Oncogene 34(37):4845–4854. https://doi.org/10.1038/onc.2014.406