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► **To cite this version:**

Arnault Tauziède-Espariat, Aurore Siegfried, Yvan Nicaise, Delphine Dghayem, Anne Laprie, et al.. PLAG1 fusions extend the spectrum of PLAG(L)-altered CNS tumors. *Acta Neuropathologica*, 2023, 146 (6), pp.841-844. 10.1007/s00401-023-02643-4 . hal-04934758

**HAL Id: hal-04934758**

**<https://hal.science/hal-04934758v1>**

Submitted on 7 Feb 2025

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## PLAG1 fusions extend the spectrum of PLAG(L)-altered CNS tumors

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Received: 18 August 2023 / Revised: 2 October 2023 / Accepted: 2 October 2023 / Published online: 23 October 2023  
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Central Nervous System (CNS) embryonal tumors with PLAG-family amplification have been isolated by a distinct DNA-methylation profile [1]. These tumors are characterized by recurrent *PLAGL1* or *PLAGL2* amplifications [1, 4]. In some cases, no amplification of these genes was found (9.7%, 3/31) [1]. Here, we report two cases, classified as being part of the “embryonal tumor with PLAG-family amplification” methylation class (MC), that did not have a PLAG-family amplification but instead harbored a *PLAG1* fusion. The aim of our work was to compare the clinical, radiological and histopathological features of these cases with previously published cases having a *PLAGL1/2* amplification.

The two observations concerned a 6-year-old boy (Case #1) and a 39-year-old woman (Case #2). The tumors were located in the left occipital lobe (Case #1) (Fig. 1a–d) and in the fourth ventricle with another location in the left

temporal lobe and a leptomeningeal dissemination (Case #2) (Fig. 1e–h). Neuroradiological review revealed large tissular and cystic tumors, having strong enhancement after contrast injection (Fig. 1). Histopathological review revealed that both cases presented similar features (Fig. 2). They were well circumscribed from the brain/cerebellar parenchyma and composed of sheets of monotonous oval cells with round to oval nuclei and a pale cytoplasm (Fig. 2a and g). In some areas, an epithelioid pattern with sharply demarcated tumor cells was present. A dense branching capillary network (with microvascular proliferation in case #2) was observed. No rosettes, rhabdoid component or pseudorosettes were discovered. Hemorrhagic and microcystic modifications were present. Necrosis was absent, but the mitotic count and proliferation index were high (Fig. 2f and l). Immunohistochemistry detected a preserved expression of INI1, BRG1 in the tumor cells but there was no immunopositivity for LIN28A

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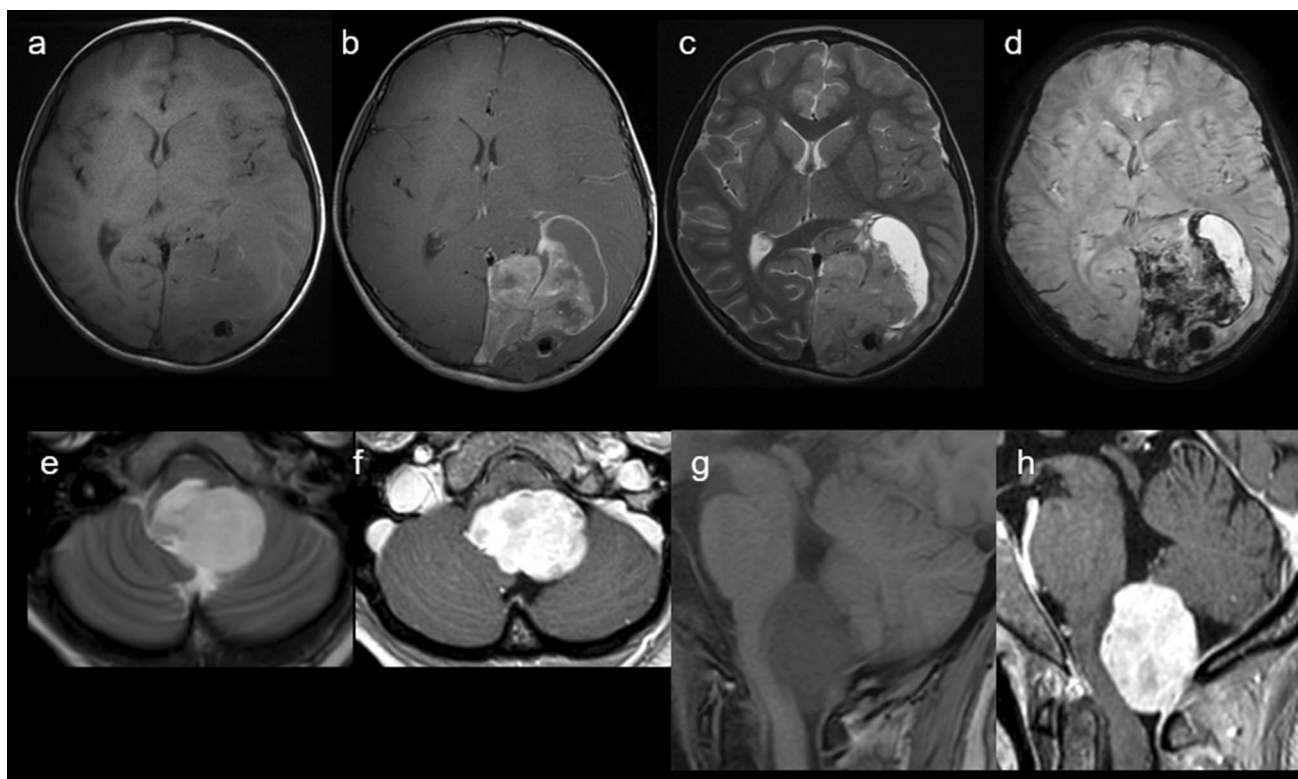
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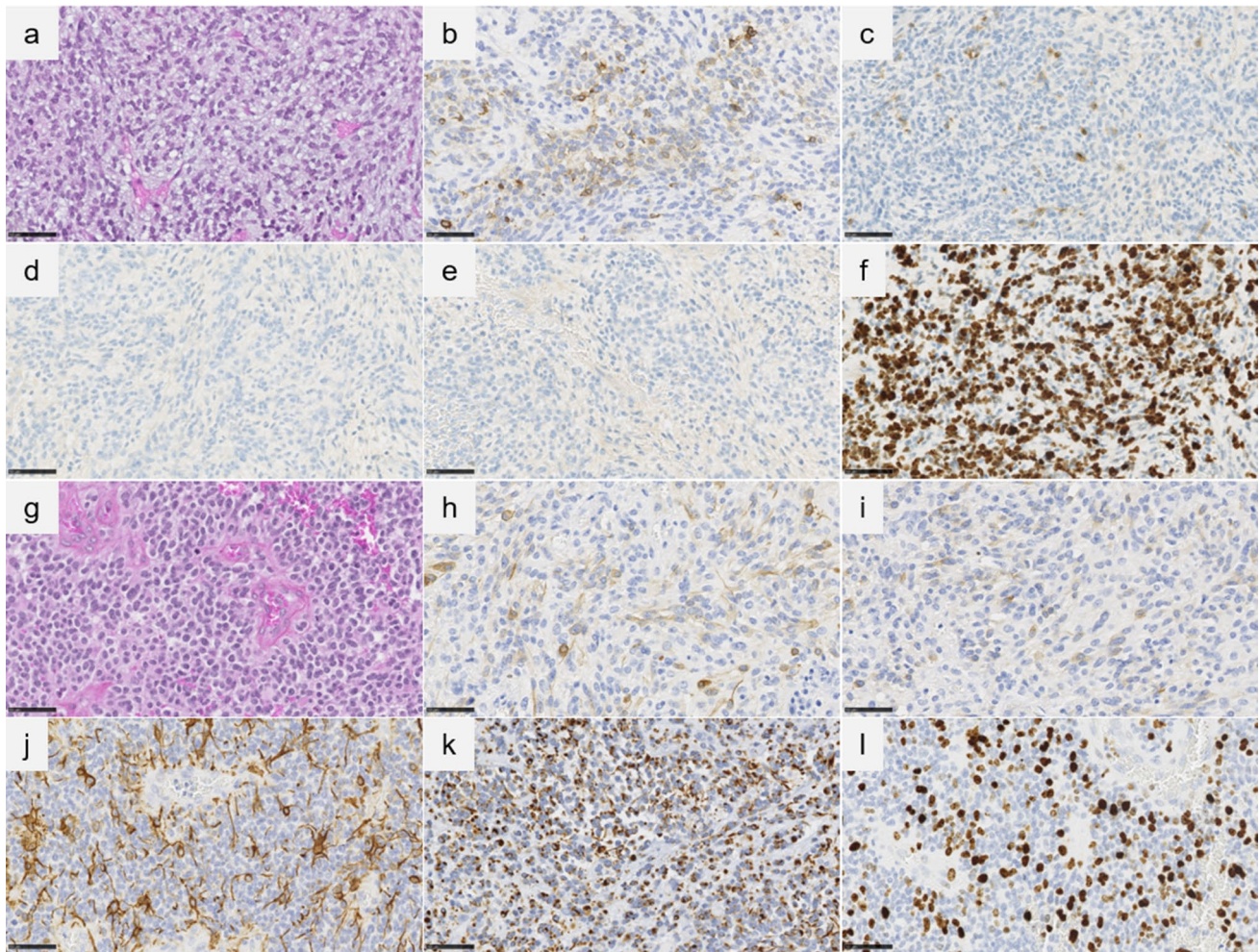
**Fig. 1** Radiological features of #cases 1 and 2. Case#1 (a–d): **a** MR images show a left occipital mass with tissue and cysts, low signal intensity on T1-weighted images, and strong contrast enhancement (**b**), heterogeneous high signal intensity on T2-weighted images (**c**) and extended hemorrhage on susceptibility-weighted images (**d**).

Case#2 (e–h): **e–g** MR images show a mass dorsally exophytic from the medulla oblongata, with high signal intensity on T2-weighted images, low signal intensity on T1-weighted images (**f–h**) and very strong and homogeneous contrast enhancement. *MR* magnetic resonance

or *BCOR*. Neuronal markers (*MAP2* and *synaptophysin*) were constantly expressed (Fig. 2b, c and h, i), whereas there was no or only focal expression of glial markers (Fig. 2d, e and j). *Desmin* was expressed in case #2 (without expression of smooth muscle actin or *myogenin*) (Fig. 2k). All of these results resembled the reported CNS embryonal tumors with *PLAG*-family amplification [1, 4]. Using the Heidelberg DNA-methylation classifier (v12.5), case #1 was classified as a CNS embryonal tumor with *PLAG*-family amplification (having a calibrated max-score of 0.99), whereas the second case did not present a significant calibrated score for a MC (despite good DNA integrity/quantity and performance of bisulfide conversion). They both clustered in vicinity of this MC by t-Distributed Stochastic Neighbor Embedding (t-SNE) analysis (Supplementary Fig. 1). RNA sequencing analysis of the two cases showed a fusion between *PLAG1* and *TCF4* (case #1) and *EWSR1* (case #2) genes (Supplementary Fig. 2). For Case #1, a gross total resection of the tumor was performed followed by craniospinal radiation therapy. A posterior fossa metastasis was discovered 8 months later and was treated by gross total resection, chemotherapy and radiation therapy. Histopathologically, the second lesion was similar to the primary tumor. The patient

was alive without novel progression at the end of follow-up, 65 months after the initial disease. For Case #2, a gross total resection of the posterior fossa tumor was performed, followed by craniospinal radiation therapy. At the latest follow-up, 16 months after the first surgery, the patient was alive without recurrence in the posterior fossa and with a stable disease in the supratentorial area.

The novel embryonal tumor with amplification of the *PLAGL1/2* genes mainly concerns children (85% of reported cases, ranging from 0 to 36 years old) and may be located all along the neuraxis (mostly hemispheric but also infratentorial and ventricular) [1, 4]. The sex ratio female: male is 1.4 [1, 4]. Radiologically, few data are available. These tumors seem to be well-circumscribed, voluminous tissular and cystic masses that show strong enhancement after injection of gadolinium [4]. Histopathologically, they are considered embryonal tumors and present a pluriphenotypic immunoprofile (with an expression of neuronal markers, focal expression of glial markers, and a frequent staining for *desmin* but without any immunoreactivity for the other myogenic markers) [1, 4]. Because of their poorly differentiated morphology, initial diagnoses were variable: glioneuronal tumors, sarcomas, medulloblastomas or high-grade gliomas,



**Fig. 2** Histopathological features of #cases 1 and 2. Case#1 (a–f): **a** Neoplasm composed of monotonous round tumor cells with microcystic modifications (HPS, magnification 400×). **b–c** A subset of tumor cells express neuronal markers (synaptophysin and MAP2, magnification 400×). **d–e** No expression of glial markers (GFAP and Olig2, magnification 400×). **f** High MIB labeling index (magnification 400×). Case#2 (g–l): **g** Neoplasm composed of monotonous

round tumor cells with mitoses and microvascular proliferation (HPS, magnification 400×). **h, i** A subset of tumor cells expressing neuronal markers (synaptophysin and MAP2, magnification 400×). **j** Residual expression of GFAP by staining of scattered tumor cells (magnification 400×). **k** Expression of desmin (magnification 400×). **l** High MIB labeling index (magnification 400×). HPS hematoxylin phloxin and saffron. Black scale bars represent 50  $\mu$ m

according to the tumor location [1, 4]. The two current cases were in line with all these clinical, radiological and histopathological features. However, contrarily to the first description, they did not harbor *PLAGL1/2* amplifications but rather a fusion implicating the *PLAG1* gene. To date, in the CNS, *PLAG*-family gene alterations have been implicated in two different tumor types. *PLAGL1/2* amplifications have been reported in a subgroup of embryonal tumors, whereas *PLAGL1* fusions have been described in ependymoma-like neuroepithelial tumor (NET) [1, 3]. Fusions of *PLAG1*, a gene of the *PLAG*-family, have not been reported in the CNS. They have been reported in several tumors, such as salivary gland pleomorphic adenoma, lipoblastoma, and myoepithelial carcinoma [2]. To our knowledge, no fusions implicating the *TCF4* and *EWSR1* genes have been

reported in these tumors. Cases of ependymoma-like NET with *PLAGL1* fusions [3] were distinct from ours in terms of location (all NET were supratentorial), histopathology (NET present frequent ependymal features) and immunohistochemistry (constant expression of GFAP in NET) [3]. Using t-SNE analysis, our cases clustered in close vicinity with the MC of embryonal tumors with *PLAGL1/2* amplifications. Three cases out of 31 (9.7%) of DNA-methylation based embryonal tumors with *PLAGL1/2* did not harbor any amplifications of these genes, and to our knowledge, *PLAG1* fusions were not explored [1]. Data concerning the outcome of patients with embryonal tumors with *PLAG*-family amplifications, seems to evidence a high rate of recurrences and a poorer prognosis in cases with *PLAGL2* amplifications [1, 4]. More reports are necessary to determine any potential

benefit of chemotherapy and craniospinal irradiation in the treatment of these rare tumors.

To conclude, we report, for the first time, two embryonal tumors with *PLAG1* fusions sharing clinico-radiological, histopathological, immunohistochemical, and epigenetic similarities to CNS embryonal tumors with PLAG-family amplification. Consequently, *PLAG1* fusions expand the spectrum of the alterations encountered in CNS tumors. Consequently, we recommend searching for alternative alterations of the *PLAG1* gene in the event of a radiological and histopathological suspicion of this diagnosis when *PLAGL1/2* amplifications have not been found.

**Supplementary Information** The online version contains supplementary material available at <https://doi.org/10.1007/s00401-023-02643-4>.

**Acknowledgements** We would like to thank the laboratory technicians at the GHU Paris Neuro Sainte-Anne for their assistance and the association “111 des arts”. The RENOCLIP-LOC is the clinico-pathological network instrumental in the central histopathological review supported by the Institut National du Cancer (INCa).

**Author contributions** AT-E, DD, AL, VL, JM, OK, VD-R, and NB: compiled the MR-I and clinical records; ATE, PR, GG, AM, FC and PV conducted the neuropathological examinations; AT-E, AS, EU-C, YN, PS and FS: conducted the molecular studies; AT-E, LH and PV: drafted the manuscript; all authors reviewed the manuscript.

**Funding** The authors declare that they have not received any funding.

## Declarations

**Conflict of interest** The authors declare that they have no conflicts of interest directly related to the topic of this article.

**Ethical approval** This study was approved by the GHU Paris Psychiatrie Neurosciences, Sainte-Anne Hospital’s local ethic committee.

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