

## **Early wound site seeding in a patient with CNS high-grade neuroepithelial tumor with *BCOR* alteration: A case report**

**Running title:** Wound site seeding in CNS HGNET-BCOR tumor

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## **Abstract**

Background: Advances in molecular profiling have facilitated the emergence of newly defined entities of central nervous system tumor, including CNS high-grade neuroepithelial tumor with *BCOR* alteration (CNS HGNET-*BCOR*). Relatively little is known about the clinical behaviour of these newly-characterized tumors.

Case description: We describe a pediatric male patient with CNS HGNET-*BCOR* who developed seeding of the tumor into the site of the surgical wound within months of surgery for resection of a residual posterior fossa tumor.

Conclusions: This case emphasises three important points. First, CNS HGNET-*BCOR* can be aggressive tumors that necessitate close clinical and radiological surveillance. Second, surveillance imaging in such cases should incorporate the surgical incision site into the field of view, and this should be closely scrutinised to ensure the timely detection of wound site seeding. Third, wound site seeding may still occur despite the use of meticulous surgical techniques.

Keywords: CNS HGNET-*BCOR*; incision metastasis; neuroepithelial tumor; PNET; embryonal tumor; wound site seeding.

## Introduction

Since publication of the latest World Health Organisation (WHO) Classification of Tumors of the Central Nervous System in 2016,<sup>1</sup> additional discrete tumor entities have emerged based on molecular profiling.<sup>2</sup> Relatively little is known about the clinical behaviour of these newly-defined tumors. Here, we report a case of the recently-characterized central nervous system (CNS) high-grade neuroepithelial tumor with *BCOR* alteration (CNS HGNET-*BCOR*) that developed seeding of the tumor into the site of the surgical wound within months of surgery for resection of a residual posterior fossa tumor. This case supports the notion that CNS HGNET-*BCOR* tumors can behave aggressively and require close clinical and radiological monitoring, with active surveillance for evidence of wound site seeding.

## Case Report

A young male presented to his local hospital overseas at the age of five with headaches and intermittent vomiting. He was found to have a right-sided cerebellar hemispheric mass with associated obstructive hydrocephalus (Figure 1A-D), and underwent subtotal resection of the lesion as well as insertion of a left ventriculo-peritoneal shunt. The lesion was initially reported as a pilocytic astrocytoma, WHO Grade I. Several months after surgery the child moved to the UK and care was transferred to our tertiary paediatric centre for oncological surveillance. Imaging performed in our institution, five months after surgery, demonstrated residual tumor (Figure 1E-H), which increased in size on a further magnetic resonance imaging (MRI) scan performed three months later (Figure 1I-L). He was asymptomatic at the time. At this stage, a decision was made to proceed to surgical excision of the residual tumor.

Magnetic resonance imaging performed post-operatively (Figure 1M-P) confirmed total resection of the residual lesion and no evidence of spinal disease. Histological analysis of the residual tumor reported a proliferative neuroepithelial tumor (WHO grade III). The child went on to receive radiotherapy to the posterior fossa (54 Gy in 30 fractions). On regular follow-up, he remained well clinically with no neurological deficits or adverse effects of treatment.

Fifteen months after completing radiotherapy, the child's parents reported a two-month history of a progressive swelling in their child's neck related to the sub-occipital midline incision. On examination, the mass was non-tender and non-fluctuant but firm. The surgical wound itself had healed well. MRI that was performed 17 months after the previous surgery

revealed a non-fluid mass, measuring 4.5 cm x 4.0 cm x 2.5 cm, sitting in the cervical fascia in the region of the previous surgery (Figures 2E and 3). On retrospective review of all the previous MRI scans, this lesion was present on imaging performed 4 months following the second procedure (Figure 2B) and had progressively enlarged since then. The patient underwent a gross total resection of the cervical mass. At surgery, a well-encapsulated soft tissue mass was identified in the deep upper cervical musculature, separate from the dura and within the caudal end of the sub-occipital incision, extending down to the spinous process and lamina of C2. Careful extra-capsular dissection was used to completely remove the lesion. To minimise any contamination of the craniotomy site, the sub-occipital incision was only opened at the caudal end. Cerebrospinal fluid (CSF) analysis did not find any definite evidence of tumor cells.

Histopathological review, including of a sample obtained from the original surgery overseas, identified cytological and immunophenotypic similarities between the soft tissue mass in the deep cervical muscles and resected intracranial residual tumor. The tumor cells possessed round to oval nuclei with cytoplasmic processes forming a microcystic network. The cervical mass differed in that there was a prominent collagenous stroma, not present in the primary lesion. The tumor cells in all resections showed nuclear staining for NeuN but were mostly negative for glial fibrillary acidic protein (GFAP) and synaptophysin. Microtubule-associated protein 2 (MAP2) and S100 protein were only detected focally. In samples from both the intracranial resections, and the cervical tumor, BCOR protein was strongly expressed in the nucleus by immunohistochemistry using a specific antibody.<sup>3</sup> Nuclear staining for INI-1 and SMARCA4 was retained (Figure 4). The main difference between the original overseas tumor sample and the subsequent ones from our center was the higher proliferation index measured by Ki67 observed in samples from the second and third surgeries, which was moderately high and present in around 10 % of tumor cells. On further analysis of genomic deoxyribonucleic acid (DNA) extracted from formalin-fixed paraffin-embedded (FFPE) tissue, an 81 bp *BCOR* internal tandem duplication of the C-terminus was identified by polymerase chain reaction (PCR) and sequencing (methods described in <sup>4</sup>) in the primary lesion confirming the diagnosis of CNS HGNET BCOR.

The patient recovered well from the procedure and was discharged on the first post-operative day. Post-operative MRI performed prior to discharge showed complete resection of the lesion (Figure 2F). He went on to receive a further 54 Gy in 30 fractions in a field covering the length of the posterior fossa and cervical incision followed by vincristine, irinotecan and temozolomide chemotherapy. At last follow-up, one year after the cervical

tumor resection, he remains clinically well, under close radiological and clinical surveillance with no evidence of further recurrence to date.

## Discussion

The recent publication of the WHO Classification of Tumors of the Central Nervous System has incorporated advances in our understanding of molecular alterations in these tumors,<sup>1</sup> but further new brain tumor entities have been described.<sup>5</sup> One new tumor type is CNS HGNET-*BCOR*, which is characterized by in-frame tandem duplications of the BCL6 corepressor (*BCOR*),<sup>2</sup> which it shares with those recently described in clear cell sarcomas of the kidney<sup>6</sup> and soft tissue tumors.<sup>7</sup> It is still unclear if these different tumors may represent local variants of the same mesenchymal tumor entity, although there is evidence to suggest that CNS HGNET-*BCOR* is unique from these other tumors because of histological features suggestive of glial differentiation, indicating it may be considered a type of neuroepithelial tumor relatively close to glioma.<sup>8</sup> Many cases show activation of the wingless (WNT) and/or sonic hedgehog (SHH) signalling pathway.<sup>2,9</sup> To date little is known about the clinical behaviour of CNS HGNET-*BCOR*. In a study that involved genome-wide DNA methylation profiling of 323 primitive neuroectodermal tumors of the central nervous system (CNS-PNETs), 34 CNS HGNET-*BCOR* tumors were identified.<sup>2</sup> These tumors were more likely to be located within the cerebellum, and, on review of survival data available, were more likely to be associated with a poorer overall survival. Three cases of cerebellar location were described in detail,<sup>4</sup> all carrying typical genomic internal tandem duplications of the *BCOR* gene and strong nuclear *BCOR* protein accumulation shown by immunohistochemistry as in this case. Two of these cases showed an aggressive behaviour despite intensive treatment with early local recurrence.<sup>4</sup> Treatment approach is complicated by the rarity of the tumor and the lack of a standard and widely-agreed treatment protocol, although optimal treatment strategies are being investigated.<sup>10</sup>

Although extremely uncommon, seeding of brain tumors to the region of the surgical incision has been described following cranial surgery for several CNS tumor types, including meningioma,<sup>11</sup> malignant gliomas,<sup>12,13</sup> gliomatosis cerebri,<sup>14</sup> meningeal sarcoma,<sup>15</sup> intracranial metastatic renal cell carcinoma<sup>16</sup> and intracranial metastatic oesophageal carcinoma.<sup>17</sup> Postulated risk factors for wound site metastasis include multiple re-operations, immunosuppression, surgical wound complications with cerebrospinal fluid fistula, and histologic grade progression.<sup>11</sup> As long-term survival of patients with several forms of CNS tumor increases, it is possible that an increase in the frequency of extraneural seeding of CNS tumors will be observed.

Although a meticulous surgical technique was employed during the surgery at our centre, the most likely aetiological mechanism of wound seeding was iatrogenic secondary to surgical intervention. Several mechanisms to minimise the risk of tumor seeding to the wound site have been proposed, including watertight dural closure,<sup>13,18</sup> calvarial reconstruction,<sup>13</sup> post-operative high-dose radiotherapy,<sup>18</sup> and the changing of instruments,<sup>13,15</sup> surgical gown<sup>15</sup> and gloves<sup>13,15,18</sup> between the intradural and extradural parts of the operation. Some authors suggest that the use of fluid for irrigation prior to wound closure facilitates wound site seeding,<sup>15</sup> but others disagree and instead suggest that it has a protective role.<sup>18</sup> The patient we describe had watertight dural closure and final irrigation with saline during both surgeries, as is standard at our center. It is difficult to ascertain the exact mechanism by which wound site seeding occurred. Given the time period between the second posterior fossa surgery and the development of wound site seeding, and the lack of evidence of any significant pseudomeningocele on imaging, it is likely that tumor cells spread to the wound site at the time of surgery. In our case, the early seeding of CNS HGNET-*BCOR* to the wound site despite meticulous surgical practices supports the notion that CNS HGNET-*BCOR* can be an aggressive tumor that necessitates close clinical and radiological monitoring even after macroscopic and radiological total resection. Active surveillance must incorporate the surgical incision site.

To conclude, the case reported here illustrates three important points. First, CNS HGNET-*BCOR* can be aggressive tumors that necessitate close clinical and radiological surveillance. Second, surveillance imaging in such cases should incorporate the surgical incision site into the field of view, and this should be closely scrutinised to ensure the timely detection of wound site seeding. Third, wound site seeding may still occur despite the use of meticulous surgical techniques.

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## Figure legends

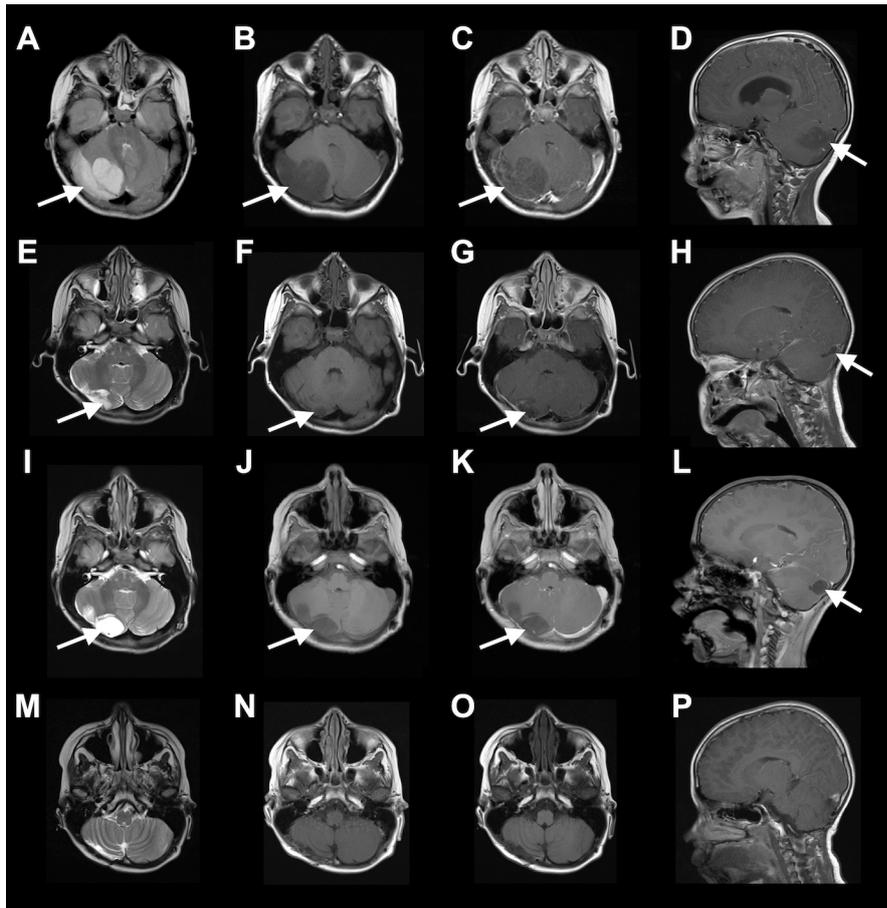


Figure 1. Axial T2-weighted (A, E, I, M), T1-weighted non-contrast (B, F, J, N), T1-weighted post-contrast (C, G, K, O), and sagittal T1-weighted post-contrast (D, H, L, P) MRI performed at different time points. A-D: Initial presentation MRI scan from overseas, prior to any surgical intervention, demonstrating a right cerebellar hemispheric mass (arrows), which is associated with partial effacement of the fourth ventricle and obstructive hydrocephalus. E-H: MRI scan performed five months following the initial surgery overseas, demonstrating residual non-enhancing solid tumor (arrows) in addition to post-operative changes in the right cerebellar hemisphere. The ventricles are decompressed following placement of a left parietal ventriculo-peritoneal shunt. I-L: MRI scan performed eight months following the initial surgery, demonstrating an increase in the volume of the non-enhancing right cerebellar hemisphere residual tumor (arrows). M-P: MRI scan performed following the second surgery to remove the residual tumor, demonstrating no evidence of tumor recurrence or residual disease.

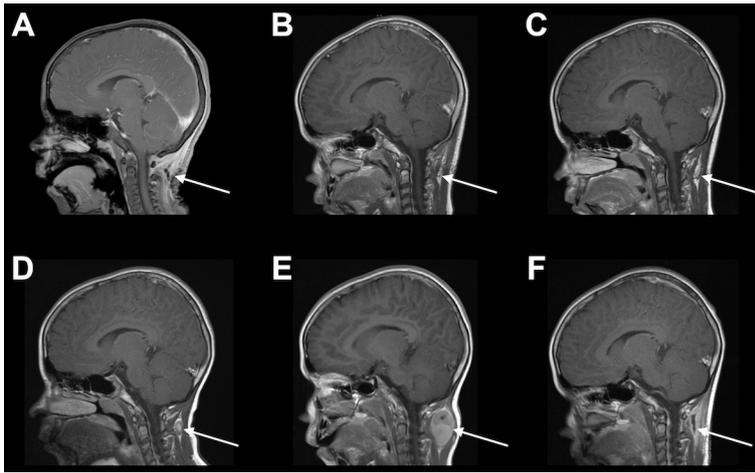


Figure 2. Sagittal T1-weighted post-contrast MRI performed at different time points following the second surgery for resection of the residual posterior fossa tumor: at 48 hours (A), 4 months (B), 10 months (C), 14 months (D), 17 months (E), and 18 months (F). Arrows indicate the location of the site of tumor seeding. A progressive increase in the size of the metastasis is visible over time (B-E), and the imaging performed less than 24 hours of surgery for the neck metastasis (F) shows complete resection of the lesion.

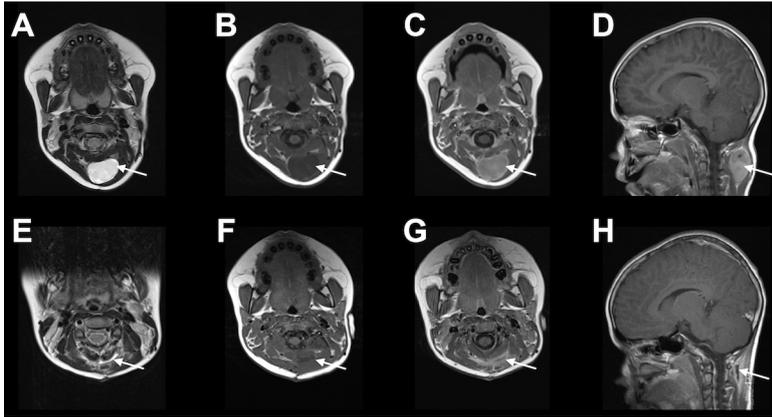


Figure 3. Axial T2-weighted (A, E), T1-weighted non-contrast (B, F), T1-weighted post-contrast (C, G), and sagittal T1-weighted post-contrast (D, H) MRI performed before (A-D) and after (E-H) resection a wound site metastasis. A-D: Imaging performed 17 months after the surgery for resection of the residual posterior fossa tumor demonstrates a soft tissue tumor in the left posterior neck deep to the surgical scar (arrows). E-H: MRI performed after surgery to the neck metastasis demonstrates complete resection (arrows) and no new adverse features.

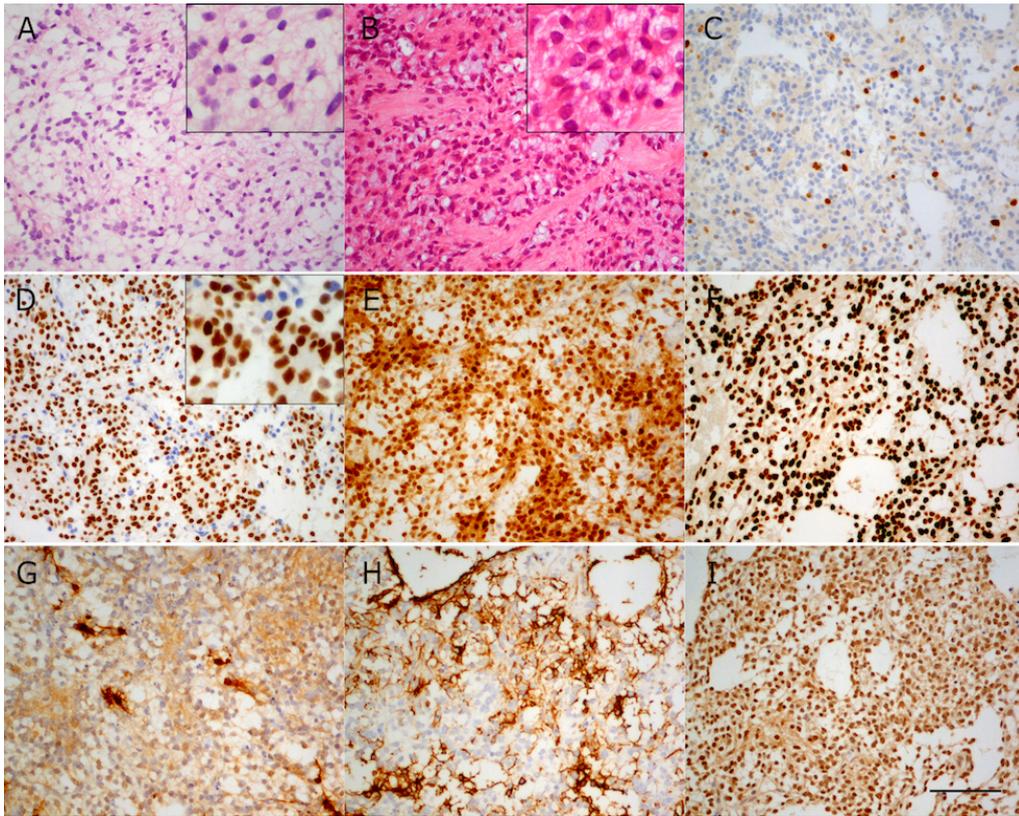


Figure 4. Representative histopathology. Hematoxylin and eosin (H&E) of primary CNS lesion (A) and incisional neck lesion (B). The following images (C-I) are from the primary CNS lesion: Ki67 staining was moderately high (C), nuclei stained positive for BCOR (D) and NeuN (E), while retaining INI-1 and SMARCA4 (F and I). Patchy focal staining was present for S100 protein (G) and MAP2 (H). Scale bar represents 100 micrometre and inserts (in A, B and D) are 100 micrometre.

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