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Case report

Extraneural metastatic paediatric glioblastoma: Case report and literature review

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ABSTRACT

The incidence of paediatric glioblastoma is uncommon in comparison to their adult counterpart. Even more infrequent are extraneural metastases in glioblastoma. A previously well 14-year-old female presented with progressive right hemiparesis secondary to a left fronto-temporal lobe glioblastoma (WHO IV). She underwent successful gross total resection for her brain tumour. Prior to commencement of her adjuvant treatment, she developed tumour recurrence associated with intra-lesional haemorrhage. Although she underwent a second surgery, the patient developed bilateral malignant pleural effusion secondary to extraneural pulmonary metastases. Early awareness of its existence enables prompt diagnosis for this devastating disease. The authors emphasize the urgent need for international collaborations to work together for children affected by this challenging brain tumour.

1. Introduction

Central nervous system (CNS) tumours constitute the largest group of solid tumours in children [1]. Although high grade gliomas (HGG) occur in all age groups, they are prevalent in adults [2]. In contrast, paediatric glioblastoma (pGBM) is uncommon, accounting for 3 to 15% of all childhood CNS tumours [3,4] and portends a poor prognosis [3–5]. As HGG is a malignant and progressive brain tumour, it is theorized that the short survival time and presence of the blood-brain-barrier are reasons why HGG rarely present with extraneural metastases [6,7]. The authors describe a unique case of extraneural metastatic GBM in an adolescent and discuss the case in corroboration with current literature.

2. Case report

A previously well 14-year-old female presented with right-sided weakness. There was no history of trauma, seizure, infection or constitutional symptoms. Upon clinical examination, she was found to have a right facial droop and right hemiparesis. The remainder of her neurological examination was otherwise unremarkable Magnetic resonance imaging (MRI) brain reported a large left frontal lobe mass with heterogeneous enhancement with perilesional oedema and midline shift. She underwent a left fronto-temporal craniotomy and excision of the intra-axial mass. Gross total resection was achieved, and a post-operative MRI scan showed no residual lesion (Fig. 1). Final diagnosis was glioblastoma (WHO Grade IV). (Fig. 2).

The patient was referred to the oncology team for adjuvant therapy. Prior to her commencing treatment, she was admitted for right-sided weakness and headaches. Computed tomographic (CT) scan of her brain demonstrated tumour recurrence with intra-tumoral haemorrhage (Fig. 3). She underwent an urgent craniotomy, clot evacuation and excision of recurrent tumour. Histology from the second surgery concurred with the previous diagnosis of glioblastoma.

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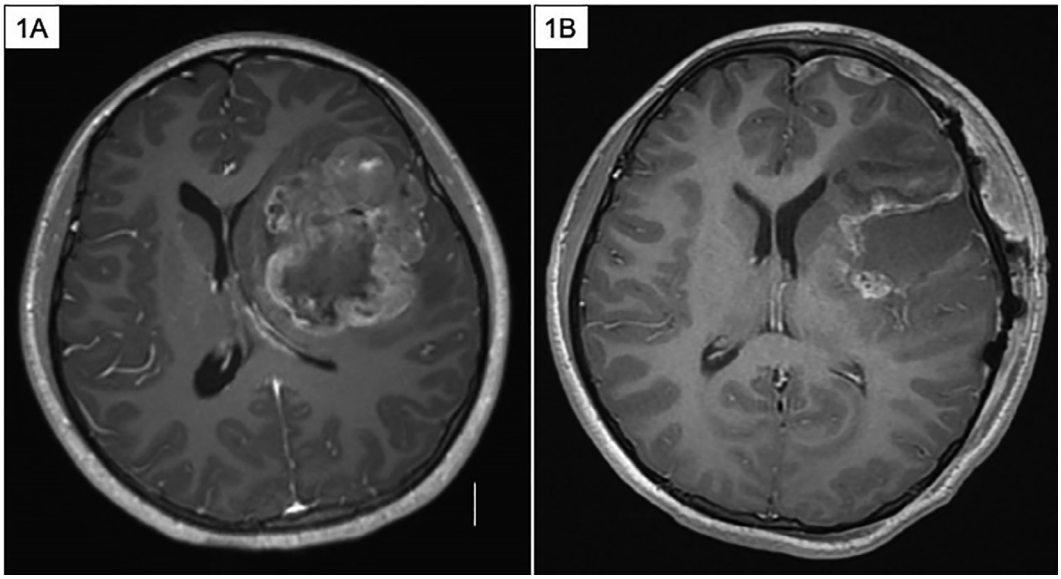

Fig. 1. (A) Representative axial, T1-weighted post-contrast MRI image demonstrating a 6.3 × 6.5 × 5.6 cm heterogeneously enhancing, lobulated left frontal lobe intra-axial mass. Within the medial aspect of the lesion, there are small, irregular non-enhancing cystic/necrotic component. Areas of susceptibility within the mass are suggestive of haemorrhage. There is perilesional oedema with mass effect resulting in effacement of the left lateral ventricle. (B) Representative axial, T1-weighted post-contrast MRI image performed on post-operative Day 1. This MRI study reported no significant residual post-contrast enhancement indicative of tumour.

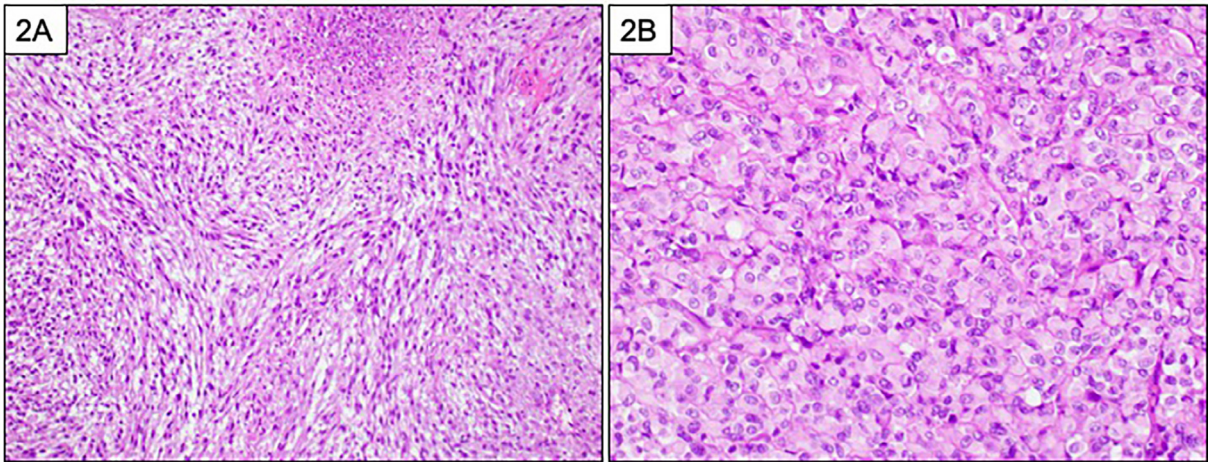

Fig. 2. (A) Haematoxylin and eosin section of tumour showing round to spindled neoplastic cells with hyperchromasia and vague fascicular to storiform architecture. Necrosis is present (×100). (B) In some areas, the neoplastic cells assumed a gemistocytic appearance (×400). Of note, subsequent immunohistochemistry was positive for S100, glial fibrillary protein (GFAP) with focal areas of p53-positivity. It was negative for IDH1 (R132H), synaptophysin, epithelial membrane antigen (EMA) and CD34. The Ki67 proliferative index was 30 to 40%.

After an uneventful 6 weeks, the patient re-presented with breathlessness. Chest X-Ray showed bilateral pleural effusions. Drainage was performed. Cytology of the pleural collection reported atypical cells reminiscent of neoplastic origin. Infective investigations for the fluid were negative. (Fig. 4). Putting it all together, the working diagnosis was that of glioblastoma with extraneural pulmonary metastases. Despite repeated interventions, follow-up chest X-rays showed worsening, loculated pleural effusions. In view of her guarded prognosis, decision was made to pursue a palliative course. She eventually demised from respiratory failure.

3. Discussion

Extraneural metastases from primary brain tumours are rare. For glioblastoma, the overall incidence of extraneural metastases is estimated to be less than 0.5% [8]. One of the main assumptions

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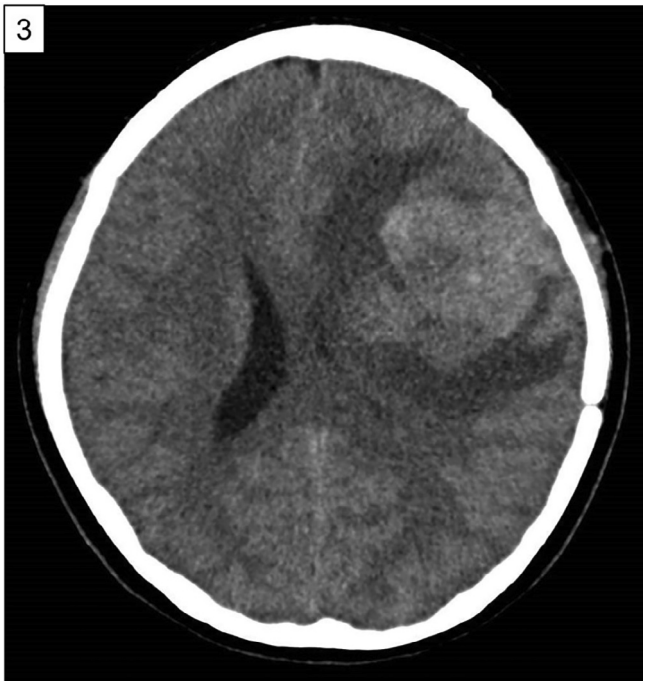

Fig. 3. Representative axial, non-contrast CT brain image showing tumour recurrence associated with intra-tumoral haemorrhage. Significant vasogenic oedema and midline shift to the right is also observed.

is that haematogenous dissemination of glioma cells is assumed t to be physiologically implausible. This is because firstly, traditional teaching cites there are no lymphatic vessels in the CNS. Next, the blood-brain-barrier is believed to function as protection against tumour penetration [9,10]. Also, surgery itself has been implicated as a putative factor facilitating tumour spread [8,11]. This is in line with previous reports that have observed direct invasion of glioma cells via the craniotomy site into adjacent dura [12,13]. Under such circumstances, it is believed that neurosurgical manipulation of the primary tumour creates a direct path for cells to be released into the haematogenous, lymphatic or subarachnoid spaces. However, this hypothesis is unproven [14]. Another well-established route for extraneural metastases in gliomas is via cerebrospinal fluid shunting [15,16]. Nonetheless, we exclude this process from the discussion as our patient does not have a shunt [10].

Advancements in molecular technologies have proven that pGBM are biologically distinct from adult HGGs. We are now aware of complex interactions between DNA methylation, histone modifications, chromatin remodelling and altered gene expression, resulting in unique transcriptome profiles for pGBM [17]. Despite better disease understanding, exact mechanisms underlying metastasis in pGBM remain unelucidated. Moving forward, clinicians need to be mindful of the possibility of extraneural dissemination in these tumours. In conclusion, we emphasize the need for international collaborations to work closely together for children affected by this devastating disease.

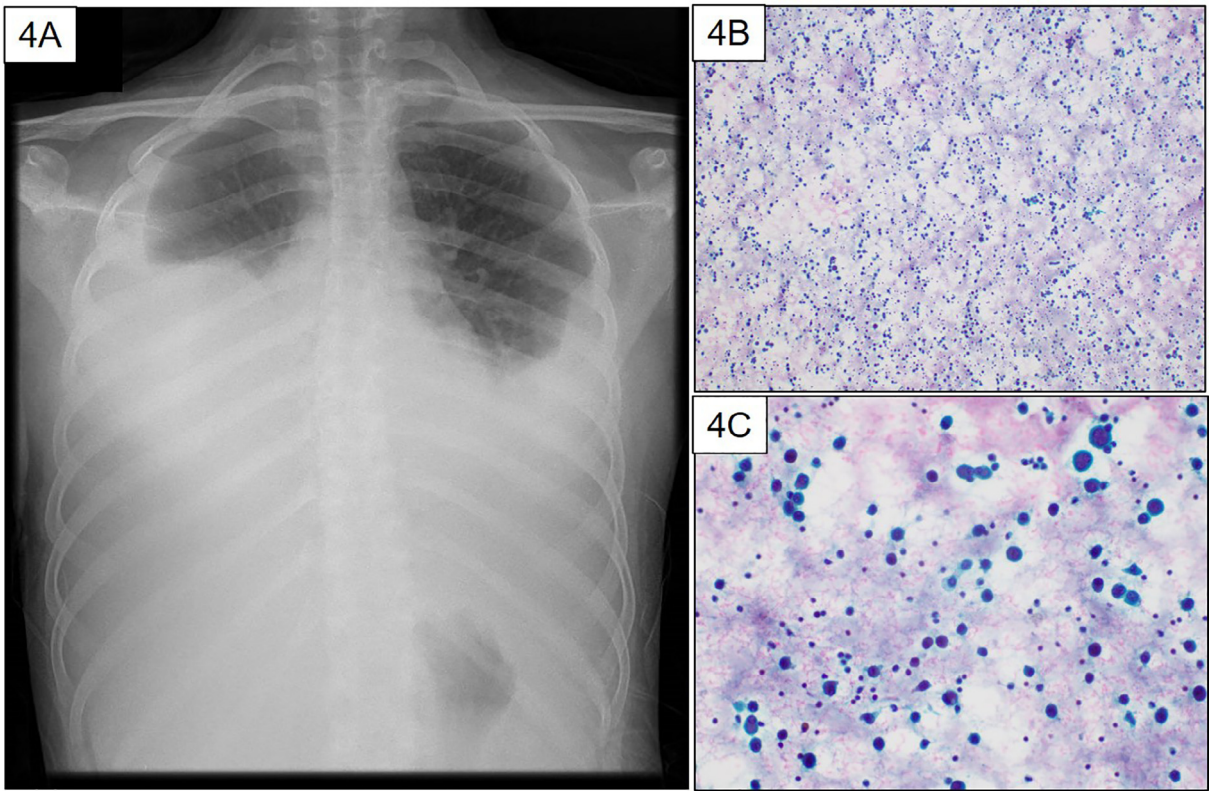

Fig. 4. (A) Chest X-ray study performed in sitting position. This shows a large right pleural effusion and moderate-sized left pleural effusion. (B) Papanicolau smear of pleural fluid shows a cellular yield of atypical cells with round nuclei (×40). (C) Higher magnification shows that these cells have irregular nuclear contours, coarse chromatin, occasional distinct nucleoli and ample cytoplasm (×200).

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