CASE SERIES

# Paediatric choroid plexus carcinoma: a retrospective case series from Karachi

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## Abstract

The objective of this study is to report clinical, radiological, and histopathological characteristics of three paediatric patients diagnosed as Choroid plexus carcinoma seen at our hospital, between 2015 and 2020.

Three patients were diagnosed with choroid plexus carcinomas between 2015 and 2018. The mean age at diagnosis was 1.3 years (range 8 months to 1.5 years). All the three patients had subtotal resection and received adjuvant chemotherapy. One patient also received adjuvant radiotherapy. Despite these treatment measures, residual disease was noted in all three patients and two patients were subsequently treated on palliative care grounds. The average duration of follow-up after the first surgery for all three patients was approximately 33 months.

Attaining satisfactory outcome in patients with CPC is challenging. Our case series reflects the difficulty in achieving gross total resection and ensuring that the disease does not recur.

**Keywords:** Choroid plexus carcinoma, Gross total resection, Adjuvant chemotherapy, Paediatric brain tumour.

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## Introduction

Choroid plexus carcinomas (CPCs) are infrequently encountered malignant intracranial neoplasms that arise from the neuroepithelium lining the cerebral ventricles. CPCs are highly aggressive tumours, with a progression free survival (PFS) rate of 13 months and median overall survival (OS) rate of 29 months[1] and 5-year survival rates between 25% and 74.1%.[2] CPCs have a predilection for paediatric population; the age at which CPCs are diagnosed ranges between 2 to 3 years.[1,3] The goal for treatment of CPCs is gross total resection (GTR). Adjunctive treatment options include chemotherapy and radiation.

CPCs are rarely diagnosed in our population, leading to variation in the management based on individual institutional protocols. This study aims to investigate the clinical, radiological, and histopathological characteristics of patients diagnosed and treated with CPCs at our hospital. Furthermore, the management course, consisting of surgery, chemotherapy, and radiation, and patient outcomes are reviewed to contribute to the existing literature.

## Case Series

The records of paediatric patients diagnosed with brain tumours between 2010 and 2020, were retrospectively reviewed for locating cases of Choroid plexus carcinomas. Patients 1 was diagnosed in August 2018 at the Aga Khan Maternal and Child Care Centre (AKMCCC), Hyderabad. Patient 2 and 3 were diagnosed in February 2016 and August 2015 at the Aga Khan University Hospital, Karachi. The clinical, radiological, and histopathological characteristics, surgical and medical interventions, and hospital course of these patients were analysed.

Summary of clinical presentation, radiological investigations, and treatment: A total of three patients were diagnosed with CPC at the Aga Khan University Hospital (AKUH) Karachi, during the study period and the details are mentioned in Table 1. Their mean age was 1.3 years (range 8 months to 1.5 years). Of the three patients, two were males, while one was female. Symptoms at presentation in all three patients were indicative of raised intracranial pressure (ICP), including vomiting, irritability and agitation, difficulty in standing or walking, and experiencing falls. One patient had delayed milestones, while another had upper extremity tremors.

Radiological investigations, including computed tomography (CT) scans and magnetic resonance imaging (MRI) of the brain, of all the patients revealed heterogeneous masses arising from the lateral ventricles. The lesions showed homogenous post-contrast enhancement and multiple flow voids suggestive of high vascularity. Perilesional oedema and evidence of mass

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**Table-1:** Summary of data for patients with CPCs in this case series

| Patient no. | Sex | Age at Dx | Symptoms at Dx | Location of tumour | Histopathological markers | Surgery | Extent of resection | Chemo | RT | Residual or recurrent disease | Metastases | Follow-up and outcome |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 1.5 years | Vomiting, agitation, gait problems, upper limb tremors | Left temporoparietal region with extension into left lateral ventricle | GFAP: PositiveCK AE1/AE3: Positive INI-1: Positive EMA and SALL-4: Negativep-53: Not performed | Supratentorial craniotomy with EVD placementLeft parieto-occipital craniotomy x 2 | Subtotal resection | 4 cycles of ICE | No | Yes | No | Placed on palliative careDied of disease after 24 months |
| 2 | M | 8 months | Vomiting, irritability, history of falls | Right lateral ventricle | Pan-keratin: PositiveINI-1: weak but retainedCK AE1/AE3: PositiveSynaptophysin: PositiveGFAP: Positivep-53: Negative | Right temporoparietal craniotomy + EVD placementRight parietal craniotomy | Subtotal resection | 1 cycle of ICE | No | Yes | Spinal metastases | Was followed for 58 months after first surgery Placed on alternative chemo regimenDied of disease after 59 months |
| 3 | F | 1.5 years | Irritability, difficulty standing, delayed milestones | Left lateral ventricle | CK AE1/AE3 and CK 7: positivep - 53: positive | Left temporoparietal craniotomy + EVD placementPlacement of Ommaya reservoir | Subtotal resection | 6 cycles of ICE | 5 fractions of Gamma knife | Yes | No | Placed on palliative care.Died of disease after 18 months |

Chemo - chemotherapy; CK – cytokeratin; Dx – diagnosis; EVD – extra ventricular drain; ICE – Ifosfamide, Carboplatin, Etoposide; RT – radiotherapy

effect such as midline shift were present in all three patients. Patient 3 had significant mass effect resulting in midline shift and impending uncal herniation.

All patients underwent initial neuro-navigation guided craniotomy with intended gross total resection (GTR)/maximum safe resection of the lesion and received adjuvant chemotherapy with the ICE (Ifosfamide, Carboplatin, Etoposide) protocol for residual or recurrent disease after surgery.

### Individual summaries of patients' management

**Patient 1:** Patient 1 had a space occupying lesion in the left temporoparietal region with intraventricular extension and no evidence of spinal disease. This patient underwent craniotomy and excision of the lesion thrice within 12 months. After the first surgery, the presence of residual disease on post-operative MRI could not be ruled out and the patient subsequently underwent four cycles of ICE chemotherapy. An MRI of the brain two months later, was highly suggestive of residual disease, leading to a second craniotomy and resection six months after the first surgery. A postoperative MRI showed extension of the lesion into the left cavernous sinus, for which a third and final attempt at resection was undertaken. However, postoperative MRI revealed evidence of a recurrent neoplastic focus in a location not seen on previous imaging. The patient subsequently underwent radiosurgery with Gamma knife delivered in five fractions. A multidisciplinary tumour board determined that a fourth attempt at resection would be futile and advised the family to pursue palliative care. Patient died of the disease after 24 months of diagnosis.

**Patient 2:** Patient 2 had a space occupying lesion in the right lateral ventricle (Figure 1A). The patient underwent a craniotomy and excision of the lesion when he was eight months old. While this patient's spine was not evaluated for the presence of disease prior to surgery, an MRI of the brain and spine performed 1.5 months after surgery revealed residual disease and possible spinal drop metastases (Figure 1B). The patient's family abandoned therapy after one cycle of ICE chemotherapy. He returned to continue his clinical care after four years; an MRI performed this time showed residual disease in the brain (Figure 1C). ICE chemotherapy was started again, and a second resection was attempted. Postoperative MRI showed residual disease in the lateral ventricle, with

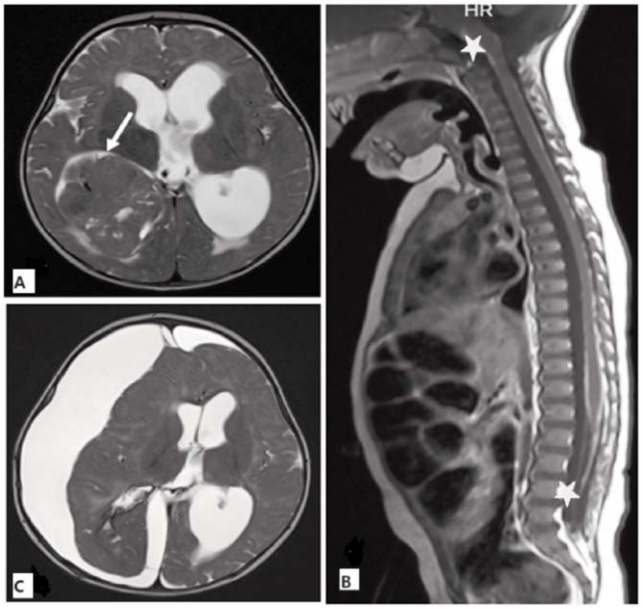


**Figure-1:** (Patient 2): Gadolinium enhanced MRI of the brain T2-weighted axial images (A, C); (A) an isointense to hyperintense and homogenously enhancing mass lesion (white arrow) in the right lateral ventricle measuring approximately 45x63x69mm with marked dilation of all ventricles representing hydrocephalus; (B) T1 spinal sagittal image showing plaque-like patchy icing sugar pattern of post-contrast enhancement along the spinal cord and medulla oblongata (stars) consistent with metastatic disease and (C) interval resection of the previously seen lesion seen with a small area of residual abnormal signal intensity and corresponding enhancement within the surgical bed in the occipital horn of the right lateral ventricle likely representing residual disease.

redemonstration of leptomeningeal carcinomatosis and perineural spread of the disease. The patient also suffered from an episode of haemorrhagic cystitis secondary to Ifosfamide. Craniospinal irradiation was discussed as a potential treatment modality, but the family decided against it. The patient was deemed to have a poor prognosis and was started on oral Etoposide for one month. The patient died of disease after 59 months of diagnosis.

**Patient 3:** Patient 3 had a space occupying lesion arising from the left ventricle. This patient underwent a craniotomy and excision of the lesion. A postoperative MRI could not rule out the presence of residual disease. This patient was given six cycles of ICE chemotherapy at a different hospital and a subsequent MRI of the brain was highly suggestive of disease progression. She underwent insertion of an Ommaya reservoir less than one year after her surgery. Her prognosis was grim, due to which she received palliative care. The patient was last seen in the hospital 16 months after her craniotomy when she was admitted for suspected pneumonia with a do-not-resuscitate (DNR) code in place. She was discharged into the care of her family on adequate pain control measures. The patient died of the disease 18 months after diagnosis.

**Histopathology:** Microscopic examination revealed multiple fragments of tumour exhibiting papillary architecture with fibrovascular cores in the papillae, lined by neoplastic cells. Frequent mitotic activity, nuclear pleomorphism, and areas of necrosis were also seen. All the specimens stained positive for cytokeratin AE1/AE3. Specimens from patients 1 and 2 showed focal positivity for glial fibrillary acidic protein (GFAP). Patient 1's specimen also showed nuclear positivity for IN1-1(BAF47) while patient 2's specimen showed weak positivity for INI-1 (BAF47) and INI-1 was not performed on patients 3's specimen. In addition, patient 2's specimen was positive for synaptophysin, had a high MIB-1 index, and was negative for p-53. Patient 2's specimen was not tested for p-53. Patient 3's specimen showed additional positivity for cytokeratin 7 and was diffusely positive for p-53 and the details of histopathology of patient 3's specimen is shown in figure 2.

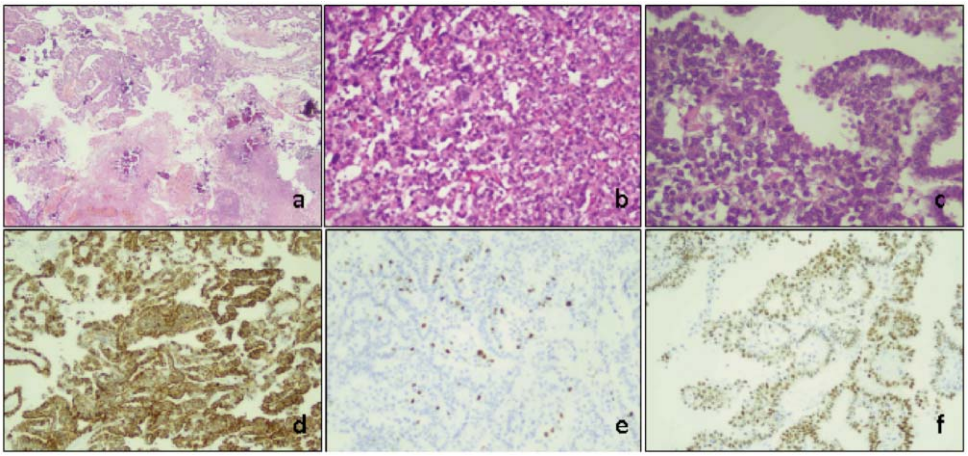


**Figure-2:** (Patient 3's Sample): A representative sample of histopathological images. (a) H&E* 4x, (a) H&E 20x, (c) H&E 40x, (d) Cytokeratin AE1, (e) Ki67, (f) p53
H&E* – Haematoxylin and eosin.

## Discussion

Choroid plexus tumours (CPTs) constitute less than 1% of brain tumours in patients of all ages[3] and 2%-4% of brain tumours in paediatric patients.[4] They are relatively more common in children, occurring in 14% of patients within the first year of life.[3] CPCs account for 34%-36% of all CPTs and are malignant and very aggressive tumours disseminated at diagnosis in more than 20% of the patients.[3,5] Of the 160 paediatric brain tumours diagnosed at our institution between 2015 and 2018, 3 (1.9%) were CPCs.

Increased cerebrospinal fluid production by the tumour and hydrocephalus due to obstruction from large tumours or impaired absorption at the subarachnoid space result in raised ICP. The patients in this study presented with signs and symptoms of increased ICP and additional neurologic symptoms due to mass effect from the lesion, like gait disturbances and focal seizures, similar to those reported in the literature.[5]

CPCs mainly occur in the atrium of the lateral ventricles in children while they are usually observed within the fourth ventricle in adults.[5] Imaging findings of heterogeneous lesions with post-contrast enhancement and high vascularity characteristic of CPCs were also present in our patients. They appear more heterogeneous than other choroid plexus tumours, due to areas of necrosis and parenchymal invasion.[6] They are usually hypointense on T1 weighted MRI images and isointense to hyperintense on T2 weighted images, with prominent post-contrast enhancement.[7]

Histopathological examination was congruent with a diagnosis of CPCs in the study patients. On histology, CPCs show features of malignancy such as papillary effacement, increased cellularity, nuclear pleomorphism, increased mitotic activity, invasion of adjacent brain parenchyma, and necrosis. CPCs may stain S-100 protein, transthyretin and GFAP, and express cytokeratins.[8] Additionally, CPCs have been associated with Li-Fraumeni syndrome.[9] Somatic TP53 mutations have been noted in 60% of CPCs which may explain the poor outcome of CPCs, as these mutations are significantly associated with increased tumour aggressiveness and worse survival.[9, 10] One of the study patients whose postoperative MRI showed disease progression that was not amenable to further treatment was observed to harbour a p-53 mutation.

The current management strategy for CPCs based on evidence from case series and expert opinions consists of GTR followed by second-look surgery, if needed, and chemotherapy and radiotherapy.[2] GTR has been shown to improve overall survival and may be one of the most important prognostic factors for CPCs.[3,11] However, aggressive cytoreductive surgery is often difficult for various reasons. The high vascularity and infiltrative nature of these tumours makes GTR a very challenging task, with complete resection achieved in 33% to 50% of cases only.[2] This is compounded by the fact that children have a very low threshold for blood loss and are, therefore, more prone to worse surgical outcomes.[12,13] Aggressive surgery may lead to debilitating and often long-lasting neurologic deficits in children. As is the case with this study, achieving GTR was difficult and the possibility of residual disease on postoperative imaging for all three of the study patients could not be excluded.

Adjuvant treatment options include chemotherapy and radiotherapy. While the efficacy of radiotherapy is not fully understood, it may be used in patients older than three years old with leptomeningeal dissemination, subtotal resection, or drop metastases. An analysis of data on CPCs from the Surveillance Epidemiology and End Results (SEER) database[14] contradicted the results of previous reports that radiotherapy conferred a significant survival benefit.[3,13] Furthermore, radiotherapy is not preferred in infants and very young children due to its severe neuropsychiatric and neuroendocrine adverse effects.

For chemotherapy, a consensus on the optimal treatment regimen does not exist although it can be used as adjuvant treatment in cases of subtotal resection and in young children in whom the goal is to avoid radiotherapy. CPC patients in the international CTP-SIOP-2000 study received a regimen consisting of etoposide, vincristine, and randomisation to Carboplatin or Cyclophosphamide,[15] while in the Head Start Consortium study they were administered either of the four chemotherapy regimens, which included drugs such as Vincristine, Cisplatin, Cyclophosphamide, Etoposide, Methotrexate, and Temozolomide.[2] The five-year survival rate for the Head Start patients was 38%, while the median OS was 62%.[2] All the patients in the current study were treated with ICE chemotherapy protocol post-surgically. It is difficult to comment on the effectiveness of this particular regimen since a consensus on the best regimen is not available.

## Conclusion

The present study highlights the relentless and lethal nature of CPCs. Subtotal resection portends a poor prognosis and adjuvant treatment with chemotherapy or radiotherapy has questionable benefits on outcomes. More studies, such as randomised controlled trials, are

needed to validate the optimal treatment protocol for CPCs.

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**Conflict of Interest:** None.

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