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ORIGINAL PAPER

The role of chemotherapy and surgical removal in the treatment of Choroid Plexus carcinomas and atypical papillomas

Annalisa Passariello[1] · Maria Tufano[1] · Pietro Spennato[2] · Lucia Quaglietta[3] · Antonio Verrico[1] · Roberta Migliorati[3] · Giuseppe Cinalli[2]

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Abstract
Introduction We performed a retrospective study on clinical assessment, tumor location, radiological imaging, histopathological characteristics, and therapeutic management of 7 patients affected by choroid plexus carcinoma (CPC) or atypical choroid plexus papilloma (ACPP) who have been observed in the last 12 years.
Methods Four patients fulfilled the criteria for classification as ACPP and three cases as CPC. The median age of the patients at the diagnosis was 42 months (range 3–190 months). Except one older patient (15 years old), all patients were younger than 3 years of age. In all patients affected by ACPP, a total surgical resection was achieved. Two children relapsed 12 and 8 months following radical removal. Both of them underwent adjuvant chemotherapy (carboplatin, cyclophosphamide, etoposide, doxorubicin, and methotrexate); a complete remission was maintained in all cases. In all three patients with CPC, it was impossible to achieve complete resection at first surgery. The response to chemotherapy was variable: in one case, it was complete with complete remission following 6 months; in one case, it was partial with reduction on volume (the patient underwent second-look surgery with complete resection); in the third case, there was no response and the patient progressed and finally died with metastatic disease, 8 months after chemotherapy was started. For children with CPC, the OS was 75 % at 6 years.
Results In our series, surgery associated with chemotherapy led to long-term survival in 4/4 patients affected by ACPP and 2/3 patients affected by CPC. Clinical results achieved in our series confirm that our therapeutic regimen is feasible and efficient as a possible adjuvant treatment for both CPC and ACPP. It also suggests that surgery has a pivotal role in the management of most children affected by CPTs.

Keywords Choroid plexus carcinoma · Atypical choroid plexus papilloma · Chemotherapy · Surgery · Central nervous system tumors · Pediatric tumors

Introduction

Choroid plexus tumors (CPTs) are intraventricular neoplasms of epithelial origin that represent about 1 % of all brain tumors and 2–4 % of brain tumors in children [18] and include choroid plexus carcinoma (CPC, World Health Organization; WHO grade 3), choroid plexus papilloma (CPP, WHO grade 1) accounting for 65–75 % of CPTs, and an intermediate form named atypical choroid plexus papilloma (ACPP, WHO grade 2) [14]. For CPP, there is a consensus concerning the treatment and radical surgical removal is considered the most ideal therapy. Regarding the other two kinds of CPTs, because of their rarity, optimal treatment has been difficult to find and current

This paper is dedicated to Roberta Migliorati MD (1955-2014), Chief of the Department of Pediatric Oncology Santobono-Pausilipon Children's Hospital of Naples, Italy.

✉ Pietro Spennato
pierospen@gmail.com

[1] Department of Translational Medicine Science, University of Naples "Federico II", Naples, Italy

[2] Department of Pediatric Neurosurgery, Santobono-Pausilipon Children's Hospital of Naples, Via Mario Fiore n. 6, 80129 Naples, Italy

[3] Department of Oncology, Santobono-Pausilipon Children's Hospital of Naples, Naples, Italy

therapeutic strategies are based on case reports and a few large cooperative studies [3, 12, 16, 29].

Complete tumor resection significantly improves the prognosis for both hystotypes (CPC and ACPP) [5, 17, 19–21, 27]. Adjuvant chemotherapy for treatment of CPC and ACPP can contribute to increasing the overall survival [1, 15, 20] and to successfully controlling the disease: it may decrease the tumor mass and increase the possibility of complete surgical removal [8]. This latter effect has recently been proposed in support of presurgical chemotherapy for patients with CPC [8].

Because of the rarity of these oncotypes, descriptions of each new case are interesting. The aim of the study is to describe seven children presenting with CPTs, who were followed by our neurosurgical and neurooncological department.

Methods

Between 2000 and 2014, 7 children received a diagnosis of ACPP or CPC, according to WHO criteria [5], at the Department of Pediatric Neurosurgery of the Santobono-Pausilipon Children's Hospital of Naples. All of them underwent neurosurgical intervention and five received chemotherapy.

Data on clinical assessment, tumor location, radiological imaging, histopathological characteristics, and therapeutic management were collected by retrospectively reviewing patients' records. All patients underwent surgery immediately after diagnosis. Chemotherapy was administered to all patients with CPC after surgery and to patients affected by ACPP if a relapse occurred after surgery. Doses, schedules, and methods of drug administration were in agreement with previously reported treatment that included four courses of systemic chemotherapy administered every 21 days. Chemotherapy included the following: (1) carboplatin 200 mg/m^2 on days 1 and 2; (2) cyclophosphamide 1.800 mg/m^2 plus etoposide 80 mg/m^2 on 1 day; (3) doxorubicin 20 mg/m^2 as a continuous infusion on days 1 and 2; and (4) methotrexate 700 mg/m^2 as a 6-h infusion on 1 day [6]. The courses were repeated until complete remission, or until total resection was considered feasible.

A second-look surgery was planned in the following situations: partial resection of primary tumor, post-chemotherapy residual tumor, or recurrent tumor, making capable a total or subtotal resection.

For all children who were available to follow up, clinical, cardiological, hematologic, audiometric, ophthalmological, neurological, and neuroradiological follow up was performed for at least 5 years after the end of the treatment.

Neurocognitive and psychomotor development has been updated using the Karnofsky Mental Scale [26].

Written informed consent was obtained by both parents prior to treatment and data gathering.

Results

Four patients fulfilled the criteria for classification as ACPP and three cases as CPC. The median age of the patients at the diagnosis was 47 months (range 3–190 months): 60 months for ACPP and 16 for CPC. Demographic and clinical details are resumed in Table 1.

ACPP

Out of the four patients harboring ACPP, two cases (cases 1 and 3) had a very acute onset due to tumor hemorrhage. The third case (case 2) had a 2-week history of visual disturbances with decreased visual acuity, and the fourth case presented signs and symptoms of intracranial hypertension (case 4—Fig. 1).

In all cases, the tumor was located in the lateral ventricles. In two cases, total resection was achieved at first surgery (case 2–4; Fig. 2). In the other two cases, first surgery allowed only a partial resection. Second-look surgery was planned 1 month later. In both cases, total resection was achieved.

Two children (cases 1 and 3) relapsed 12 and 8 months following radical removal. Recurrences were asymptomatic and were discovered at neuroradiological follow up examinations. One case (case 3) relapsed only in the surgical field and was reoperated on for radical removal, the other case (case 1) relapsed in the surgical field and presented metastasis in the infundibular recess of the third ventricle. Both of them underwent adjuvant chemotherapy as previously reported; a complete remission was maintained in both (mean follow up 114 months).

Hydrocephalus, when present, was managed by steroids and early surgery. One patient (case 4) developed subdural hygroma following resection that was managed with subduro-peritoneal shunt.

In summary, two patients were cured by surgery alone, two patients by surgery (multiple procedures, with the aim to achieve total resection) and adjuvant chemotherapy (Table 1).

CPC

All the patients affected by CPC were younger than 3 years of age at diagnosis (3, 22, and 24 months of age). Two (cases 5 and 6) presented with signs and symptoms of intracranial hypertension, secondary to acute hydrocephalus. This was managed urgently by endoscopic third ventriculostomy (ETV) in case 5, in which preoperative MRI showed aqueductal stenosis secondary to distortion of the posterior third ventricle, and by ventriculo-peritoneal shunt (VPS) in case 6 in which the aqueduct was not compressed. Cerebral and spinal metastases were ruled out at diagnosis

Both patients underwent tumor removal few days following hydrocephalus control. Partial resection was achieved in

Table 1 Characteristics of patient with atypical choroid plexus tumors and choroid plexus carcinomas

Case *n* and sex	Age at presentation (months)	S&S	Hydrocephalus (Yes/No) /Its management	First surgery CR/IR	Histology	Adjuvant CT	Second or third surgery CR/IR	OS (months)	EFS (months)	Residual focal deficit and KI (%)	Status
1 M	8	Tense anterior fontanel inconsolable crying marked hypotonia	Yes (Urgent tumor removal)	IR	ACPP	Yes	CR	120	108	−100	Alive
2 F	190	Papilledema left exophory	No	CR	ACPP	No	–	79	79	Left reduction in visual acuity 100	Alive
3 F	32	Hemiplegia, loss of consciousness, anisocoria	No	IR	ACPP	Yes	CR	144	136	−100	Alive
4 F	13	Macrocephaly, tense anterior fontanel, hypotonia, VI nerve palsy	Yes (Urgent tumor removal. + EVD[a])	CR	ACPP	No	–	20	20	−100	Alive
5 M	24	Shaking, ataxia papilledema	Yes (ETV)	IR	CPC	Yes	CR	82	82	−100	Alive
6 M	3	Macrocephaly, papilledema, tense anterior fontanelle, hypotonia	Yes (VP shunt)	IR	CPC	Yes	–	162	162	−70	Alive
7 F	22	Ataxia, VII nerve palsy	Yes (Tumor removal, followed by ETV, followed by VP shunt)	IR	CPC	Yes	IR	9	8	Hypoacusia, VII nerve palsy, hypotonia/ unavailable	Dead

CT Chemotherapy, *CR* Complete Removal, *IR* Incomplete Removal, *CPC* Choroid Plexus Carcinoma, *ACPP* Atypical Choroid Plexus Papilloma, *OS* Overall Survival, *EFS* Event Free Survival, *KI* Karnofsky Index, *ETV* endoscopic third ventriculostomy, *VP* shunt (ventriculo-peritoneal shunt), *EVD* external ventricular drainage

[a] EVD was removed. The patients developed subdural hygromas, managed with subduro-peritoneal shunt

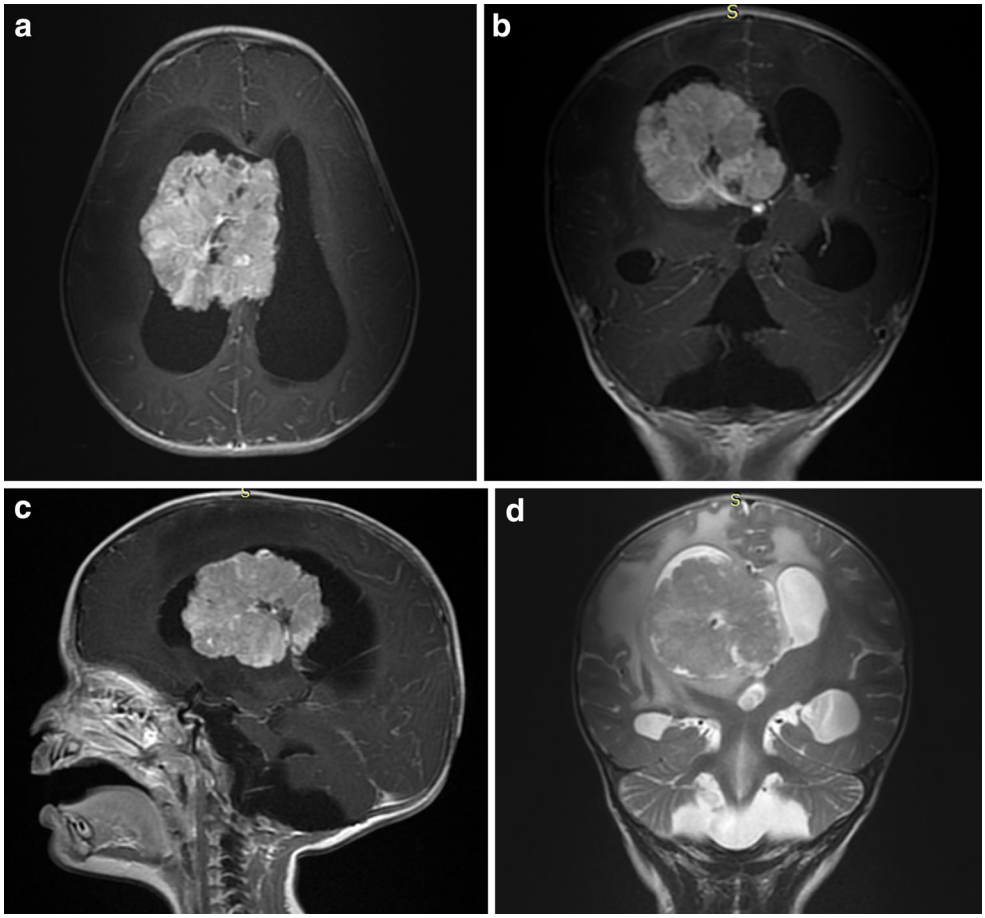

Fig. 1 Case 4. 13-month-old baby girl presenting with hypotonia, no gaze pursuit, full bregmatic fontanel, right VI cranial nerve palsy. Brain MRI showed a 6 cm in diameter well-defined tumor in the right lateral ventricle displacing the midline structures to the left side with strong heterogeneous enhancement. **a**, **b**, and **c**: preoperative contrast-enhanced T1 weighted MRImages, on axial, coronal, and sagittal planes. D: coronal T2 WI: Note the perifocal white matter edema in the ventricular walls and in the thalamus. The patient underwent complete removal of the tumor (atypical choroid plexus papilloma), through transcallosal approach. An EVD was left in the lateral ventricle and removed on the 4th postoperative day. Postoperative course was characterized by transient hemiparesis (completely resolved in few weeks), disappearance of the right sixth cranial nerve palsy, reappearance of gaze pursuit. She developed bilateral subdural hygromas, treated with subduro-peritoneal shunt

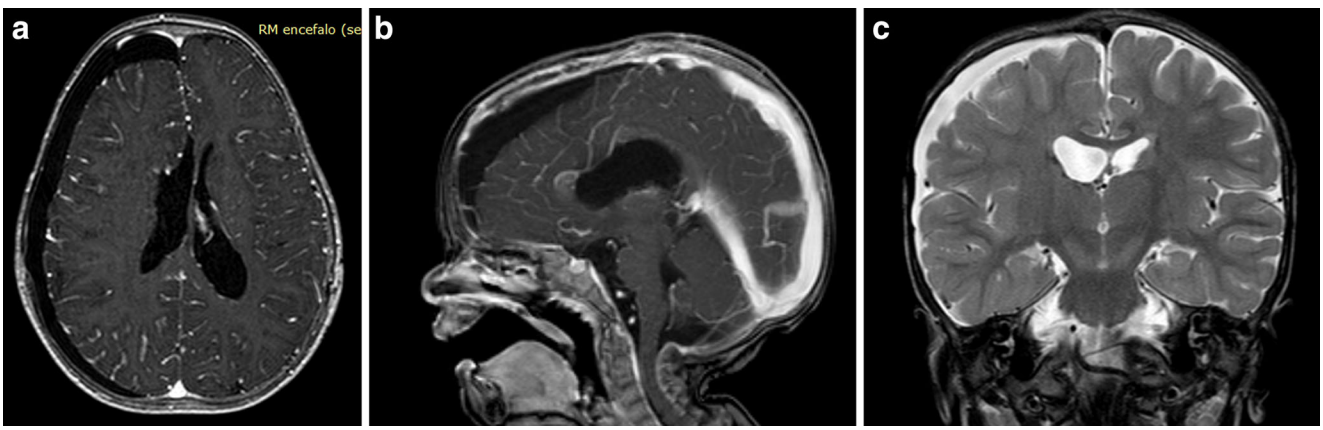

Fig. 2 1-year follow up of the same case as Fig. 1. Axial (**a**) and Coronal (**b**) contrast-enhanced MRI showed complete resection of the lesion with no recurrences. Coronal T2 WI MRI (**c**) showed resolution of perifocal edema

both. Following histological diagnosis of CPC, chemotherapy was started. In case 5 (Fig. 3), the best response was achieved at 4 months from the onset of treatment with a reduction of approximately 30 % of the initial volume. Two further MRI

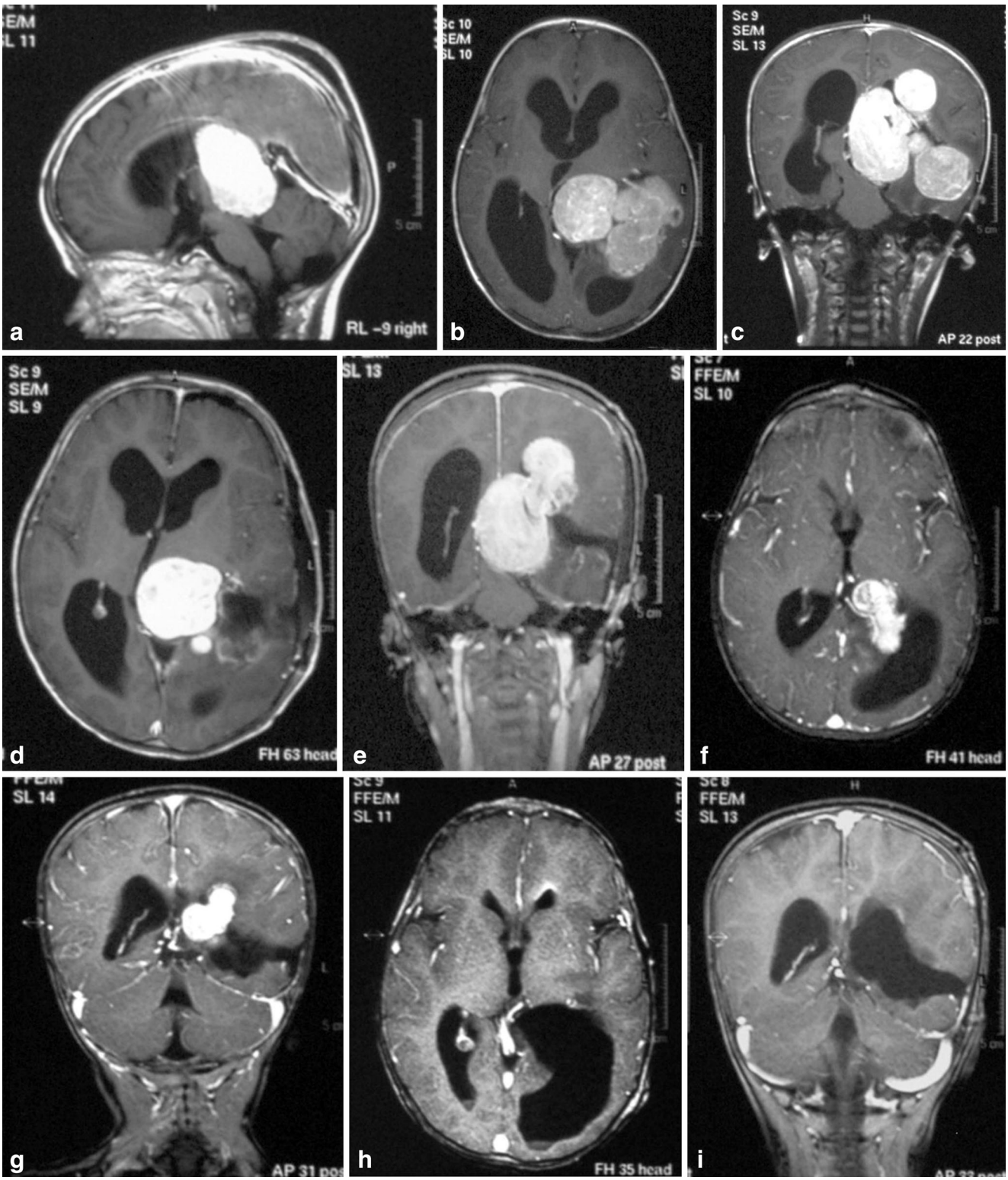

Fig. 3 Huge left lateral ventricle choroid plexus carcinoma (Case 5). Sagittal (**a**), coronal (**b**), and axial (**c**) contrast-enhanced T1 weighted MR images at presentation. Note hydrocephalus secondary to aqueductal stenosis on midsagittal image (**a**). Coronal (**d**) and axial (**e**) images following first surgery (partial resection). Coronal (**f**) and axial (**g**) images following 6 cycles of chemotherapy, showing reduction of the residual mass. Coronal (**h**) and axial (**i**) images following second-look surgery, showing complete resection

controls at a 4-month-interval showed no further reduction. The patient was then referred to surgery and a complete removal was achieved by two-step surgical intervention (with 1-month interval). Histopathological examination confirmed the diagnosis of CPC and a clear decrease of cellular proliferation index from 30 % at first surgery and 5 % on posttreatment samples was observed, in the absence of chemo-induced modifications.

In case 6, a progressive shrinkage of tumor was observed. After 6 months, complete remission was obtained and maintained with chemotherapy alone, continued during 5 further months. He is actually in continuous complete remission with a severe delayed mental development.

The patient of case 7 was a 22-month-old baby girl, which presented with ataxia, left facial nerve paralysis, drowsiness, and mydriasis in left eye. Urgent MRI showed huge tumor in the carrefour of the left lateral ventricle, with midline shift. She underwent urgent surgery, with partial resection of the lesion. In the postoperative period, the patient presented acute hydrocephalus, secondary to aqueductal stenosis. An ETV failed, therefore a VPS was inserted. Before starting scheduled chemotherapy, the patient deteriorates again because of mass effect of the residual tumor (edema and increased midline shuft). The patient was operated again on emergency basis. Only a partial removal was achieved; nevertheless, the patient improved and was able to start chemotherapy. Despite chemotherapy, the tumor progressed and metastasized. She died 8 months after chemotherapy was started.

Discussion

The management of CPTs is a challenge because they usually arise at a very young age. Due to the intraventricular localization, the tumor always grows to giant dimensions with little or no neurological signs; arterial supply is always very generous from choroidal vessels and drainage is done through very large veins into the internal cerebral veins system. The diagnosis is usually obtained in critically ill patients because of acute tumor bleeding or acute intracranial hypertension induced by obstructive hydrocephalus. Emergency surgical intervention is usually necessary at presentation to resolve the intracranial hypertension. Tumor surgery can be extremely challenging and hazardous due to the significant blood loss. Preoperative embolization of the tumor vessels has been proposed, but it is usually ineffective to achieve complete control of the bleeding due to the numerous small caliber arterial feeders [17, 21, 27]. Complete resection of tumor is the primary goal as gross total resection has been reported to improve overall survival both in ACPP and CPC; however, complete resection can be achieved in only 40 to50 % of children [30].

Due to its complexity, it is necessary to adapt the treatment to every single patient.

Among choroid plexus neoplasms, ACPP and CPC are very rare. In regard to OS and EFS, little information may be acquired from literature because as time goes on imaging techniques, surgical management, and chemotherapy regimens are changed and improved; furthermore, the last WHO classification has more strictly defined new histopathological criteria for distinguishing different subtypes of CPTs. The histological characteristic of CPC are mitotic activity, increased cellularity, nuclear pleomorphism, blurring of papillary growth pattern and necrosis. ACPP is defined as choroid plexus papilloma with increased mitotic activity. Two or more mitoses per 10 HPF can establish the diagnosis of ACPP [10].

ACPP seems to be more amenable to be cured, also in case of recurrences and metastases [16, 25, 29], even if its treatments guidelines have not been well established in the literature. Some studies suggested that adjuvant therapy, radiation alone, or radiation along with chemotherapy, may decrease the incidence of local recurrence and improve long-term survival [11]. The efficacy of chemotherapy is difficult to discuss, because the data of the literature are limited to small series or case reports. Our series suggests that ACPP can be treated with surgery alone and that chemotherapy is effective in recurrent cases. Complete resection is the goal of treatment. In case of partial resection, second-look surgery is indicated if radical resection is possible. Chemotherapy should be considered only in unresectable or recurrent tumors. In our series, total resection was achieved in all cases (following single operation in two cases and following staged surgery in two cases). Two patients were cured with surgery alone; the other two presented recurrent disease (local recurrence in one case, intraventricular metastasis and local recurrence in the other one). Both responded very well to adjuvant chemotherapy (with the same protocol as for CPP [6]), with long-term (more than 10 years) complete remission.

Treatment of CPC is more standardized. Complete resection significantly improves outcome also in case of CPC.

The 5-year survival rate is approximately 58 % after complete tumor resection and only 20 % after partial resection [23]. One way to achieve optimal resection of highly aggressive and vascular CPCs is to use a two-stage surgical approach, where an initial biopsy or partial resection and neoadjuvant chemotherapy is followed by a definitive surgery [13, 23]. Microsurgical technique may improve surgical outcome, above all early cauterization of the vascular supply (both arterial and venous).

In a recent meta-analysis, Sun et al. found that adjuvant therapy improved significantly overall survival: both combined chemo-radiotherapy as well as chemotherapy alone improved OS, but radiation alone did not [22]. In patients younger than 3 years of age, radiotherapy is detrimental; therefore, chemotherapy represents the best adjuvant modality for the

majority of patients [2, 7, 9, 28, 29]. There is no standardized chemotherapy protocol for CPC, but different drugs have been used (Table 2).

For CPC, recent reports establish an OS rate between 50 and 70 % at 2 years [12, 16, 29]. Among eight patients reported by Koh affected by CPC, the progression-free survival involved 50 % of patients in the first year and 0 % in the second year: this means that nobody was disease-free at 24 months [12].

Better results are reported by Lafay-Cousin et al. with a survival of 70 % of patients affected by CPC at a median follow up of 6.9 years: 8 of 11 patients had been treated by neoadjuvant chemotherapy and delayed second-look surgery for incomplete initial resection [13]. In our series, two out of three patients affected by CPC are alive without recurrences at 6 years.

The response to chemotherapy of CPC was variable in our small series. In all three patients, it was impossible to remove more than 50 % of initial tumor at first operation, chiefly because of intraoperative blood loss. The residual tumor responded well to chemotherapy in two cases: in one patient, complete remission was achieved following six cycles; in the other chemotherapy on residual tumor determined a 30 % reduction of tumor volume registered within 6 months from the onset. Further chemotherapy was not able to induce additional shrinkage. Therefore, the patient was addressed to surgery with the aim of total removal. This was achieved with staged surgery. Chemotherapy facilitated surgery, reducing the mass volume and its hemorrhagic nature. On histopathological evaluation, a marked decrease of mitotic index valued was observed. This supports the hypothesis that chemotherapy could play a specific antiproliferative role but has no bearing on differentiating or cytolytic effect. The same observation is reported in literature [13, 24]. The length of adjuvant chemotherapy or the timing of definitive surgery is questionable; we observed the most significant reduction of tumor volume in the first 6 months of treatment. Our experience corroborates what was already reported: second-look surgery cannot be preplanned and the most effective duration of chemotherapy is uncertain. We agree with other authors that, in case of initial partial resection, no more than four to six courses of cytotoxic drugs are needed before second-look surgery. Imaging results can guide the decision in a multidisciplinary approach [13].

In our series, we administered the same therapeutic regimen described elsewhere, based on association of carboplatin, cyclophosphamide, etoposide, doxorubicin, and methotrexate [6]. We confirm the high manageability of this regimen with few side effects, mild toxicity, and absence of late sequelae. Nevertheless, one patient progressed during chemotherapy and finally died of tumor metastases. More aggressive strategies such as myeloablative chemotherapy with autologous stem cells

Table 2 Chemotherapy in published studies for CPC patients from Zaky et al. [30] modified

Author	Patients	Median age (months)	Chemotherapy (CT)[a]/High dose chemotherapy (HDCT)[b]	Radiotherapy	Outcome
Chow, 1999 [5]	10	12	CT	50 % (at progression)	Mean survival 48 months (range 3–153)
Grundy, 2010 [9]	15	10	CT	26 % (at progression)	3 years PFS 21.7 % and OS 26.7 %
Wrede, 2009 [29]	34	27	CT	61 %	5 years PFS 28 % and OS 36 %
Lafay-Cousin, 2010 [13]	14	19	CT	21 %	5 years PFS 53.3 % and OS 74.1 %
Geyer, 2005 [7]	9	18	CT	N/A	3 years OS 63 % and PFS 33 %
Berger, 1998 [2]	7	22	CT	43 %	5 years OS 71 %
Koh, 2014 [12]	8	34	50 % CT 50 % HDCT	50 %	1 year OS: 62.5 % 2 years OS 42.9 %
Zaky, 2015 [30]	12	19	HDCT	42 % (at progression)	5 years PFS 38 % and OS 62 %
Present series	3	16	CT	No	2 alive at 5 year 1 dead

[a] Adjvant chemotherapy based on various association of chemotherapeutic agents including vincristine, etoposide, platinum analogues such as cisplatin or carboplatin, and DNA alkylating agents such as cyclophosphamide or ifosfamide

[b] High-dose chemotherapy with autologous peripheral blood stem cell transplantation

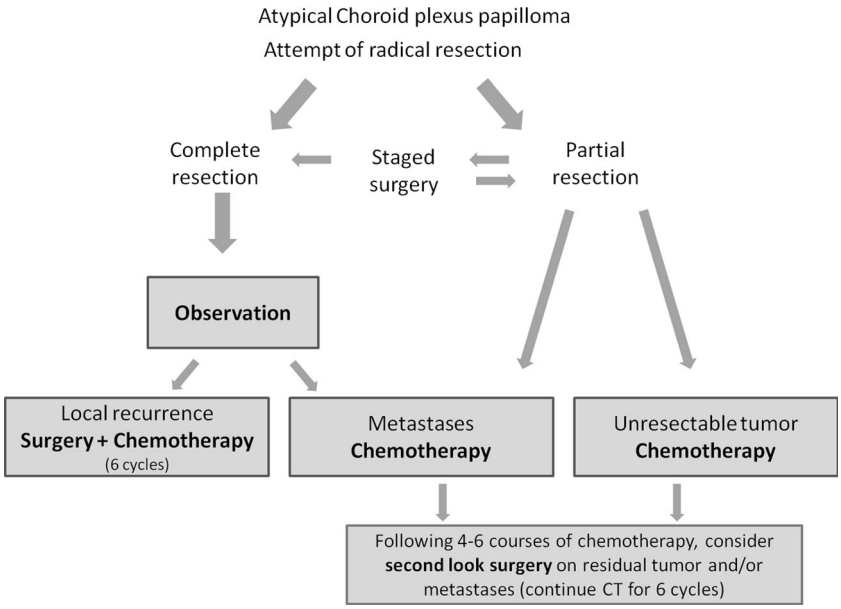

Fig. 4 Treatment algorithm for atypical choroid plexus papilloma, in our series

rescue were not considered in this case because of the poor neurologic and systemic condition of the baby.

The recent published Head Start Experience, in which 12 children with CPC (3 with disseminated disease), were treated with maximal surgical resection followed by five cycles of intensive induction followed by consolidation myeloablative chemotherapy with autologous hematopoietic stem cell rescue (± irradiation based on the patient's age and evidence of residual disease), was encouraging in term of 3- and 5- and overall survivals (83 and 62 %, respectively) [30]. However, only five patients were irradiation-free and disease-free at the end of follow up; 58 % of patients developed tumor progression/recurrence and only one patient of the seven who progressed was successfully salvageable with radiotherapy. As the same authors asserted, in this study, the additive role of myeloablative chemotherapy was not clear [30].

It is difficult to select patients affected by CPC who can ab initio benefit from megatherapy with autologous peripheral stem cell transplantation. Tabori et al.[24] demonstrated a correlation between specific mutations of the TP53 tumor

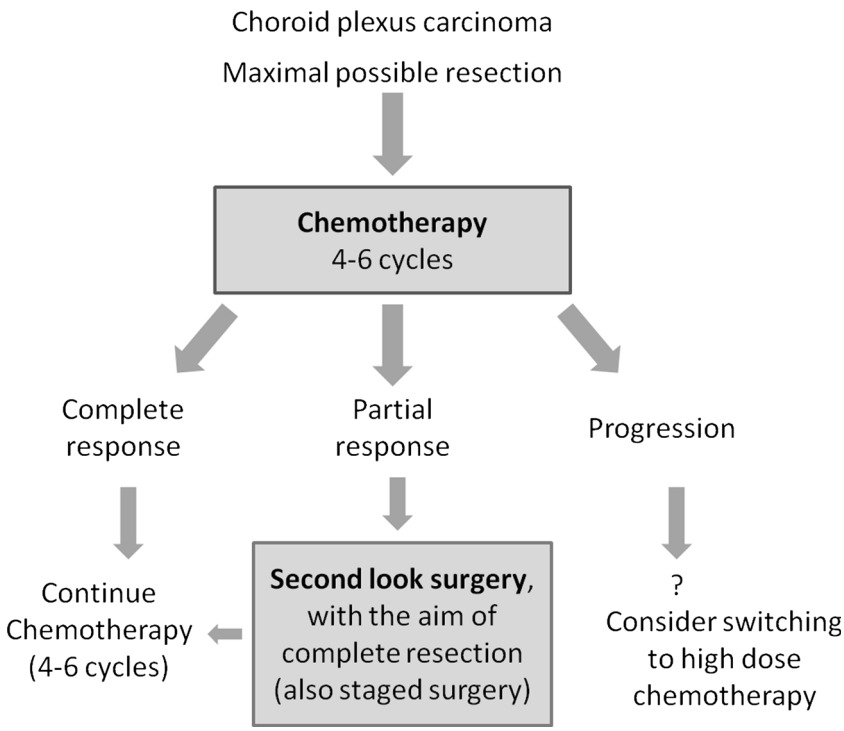

Fig. 5 Treatment algorithm for choroid plexus carcinoma, in our series. Radiotherapy is not included in the scheme because our patient were all younger than 3 years of age

suppressor genes found in CPTs genomes and poor outcome (5-year survival rates 0 % for patients positive for TP53 vs 82 ±9 % for patients negative to immunohistochemistry)

Tabori's findings have been confirmed in the last 3 years by further molecular studies. Castelo-Branco et al. identified an epigenetic mechanism of hypermethylation upstream of the transcription start site that occurs in all malignant pediatric brain tumors expressing TERT promoter. In particular, the hypermethylation, when present, determines progression of ACPP to CPC [4, 24]. With better knowledge surrounding the biology of CPTs, it will become possible to divide patients into different risk protocols: patients harboring genetic unfavorable parameters will be assigned to a more aggressive management, comprehensive of high-dose chemotherapy and eventually radiation therapy; a less intensive approach, similar to our regimen, will be recommended for patients without unfavorable genetic markers.

Hydrocephalus is a common associated feature in case of choroid plexus tumor. It can occur at presentation or during the course of the disease, especially in the immediate postoperative period and at progression. In some cases, it can be considered obstructive in nature, secondary to obstruction of the aqueduct in case of third ventricular tumor, or to dislocation of the thalamus-midbrain and distortion of the aqueduct in case of huge lateral ventricular tumor. In these cases, ETV may be an alternative to shunting. In our series, ETV was attempted twice and was successful in one case. Two patients were shunted.

Conclusions

We described the feasibility and effectiveness of a chemotherapy protocol as an adjuvant treatment to surgical tumor removal in the management of CPC and ACPP. The treatment algorithm has been summarized in Figs. 4 and 5. Our results on a small series warrant further studies to evaluate and confirm the role of adjuvant and neoadjuvant chemotherapy and to better understand the timing of surgery in these rare tumors.

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