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Neoadjuvant Chemotherapy for Facilitating Surgical Resection of Infantile Massive Intracranial Immature Teratoma

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Immature teratoma (IMT) is the most frequent histological subtype of infantile intracranial teratoma, the most common congenital brain tumor. IMT contains incompletely differentiated components resembling fetal tissues. Infantile intracranial IMT has a dismal prognosis, because it is often inoperable due to its massive size and high vascularity. Neoadjuvant chemotherapy has been shown to be effective in decreasing tumor volume and vascularity to facilitate surgical resection in other types of infantile brain tumors. However, only one recent case report described the effectiveness of neoadjuvant chemotherapy for infantile intracranial IMT in the literature, even though it is common entity with a poor prognosis in infants. Here, we describe the case of a 2-month-old male infant with a very large intracranial IMT. Maximal surgical resection was first attempted but was unsuccessful because of severe intraoperative hemorrhage. Neoadjuvant carboplatin and etoposide (CARE) chemotherapy was then administered with the aim of shrinking and devascularizing the tumor. After neoadjuvant chemotherapy, tumor size did not decrease, but intraoperative blood loss significantly decreased and near-total resection was achieved by the second and third surgery. The patient underwent adjuvant CARE chemotherapy and has been alive for 3 years after surgery without tumor regrowth. Even when neoadjuvant chemotherapy does not decrease tumor volume of infantile intracranial IMT, surgical resection should be tried because chemotherapy can facilitate surgical resection and improve clinical outcome by reducing tumor vascularity.

Keywords: immature teratoma; infantile brain tumor; intraoperative hemorrhage; neoadjuvant chemotherapy; tumor vascularity
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Introduction

Intracranial teratoma, one of the histological subtypes of intracranial germ cell tumors (GCTs), differentiates along all 3 germ layers: ectoderm, endoderm, and mesoderm. It is subdivided into 3 histological subtypes: mature teratomas (MTs), immature teratomas (IMTs), and teratomas with malignant transformation. MTs are composed exclusively of fully differentiated tissue elements, whereas IMTs contain incompletely differentiated components resembling fetal tissues (Louis et al. 2007).

Intracranial teratoma accounts for 4.9-6.3% of infantile brain tumors (Di Rocco et al. 1991; Brown et al. 1997; Rivera-Luna et al. 2003; Larouche et al. 2007). It is the most common congenital brain tumor and accounts for 29.6-36.5% of all cases (Wakai et al. 1984; Isaacs 2002). IMT is the most common histological subtype in infants (Isaacs 2004).

Intracranial teratoma in infants has a very poor prognosis, because extensive lesions are usually present at diagnosis. Most cases result in stillbirth or death shortly after birth (Isaacs 2002, 2004). Surgical excision is possible only in cases with relatively small lesions (Ulreich et al. 1993; Erman et al. 2005). The overall survival rate of infants with congenital intracranial teratomas is 7.2-12%, which is one of the lowest rates among patients with congenital brain tumors (Wakai et al. 1984; Isaacs 2002, 2004).

Neoadjuvant chemotherapy followed by surgical resection is an effective therapeutic strategy for many types of infantile brain tumors. It is known to decrease tumor volume and vascularity and facilitate surgical resection of hypervascular tumors (Lafay-Cousin et al. 2010; Van Poppel et al. 2011; Schneider et al. 2015). However, to our knowledge, only one case report in the literature described this treatment strategy for intracranial teratoma in infants (Fukuoka et al. 2014).

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Here, we present the case of a 2-month-old male infant with a very large intracranial IMT, who was administered neoadjuvant chemotherapy after the first surgical resection failed, which enabled a successful subsequent surgical resection.

Case Presentation

A 2-month-old male infant presented to our institution with a 1-month history of increasing head circumference. The patient had been a full-term infant without any perinatal problems. His family history was unremarkable. His head circumference was 33.0 cm at birth (50th percentile), 37.5 cm after 1 month (75th percentile), and 48.6 cm after 2 months (above 97th percentile).

On examination, the patient was markedly lethargic with distended scalp veins and tense and bulging anterior fontanel. Localized neurological deficits were not found. Cranial computed tomography (CT) revealed a massive supratentorial tumor containing small calcifications and surrounded by enlarged lateral ventricles (Fig. 1A). On cranial magnetic resonance imaging (MRI), the mass measured 12.8 × 10.3 × 8.1 cm and occupied approximately half of the intracranial volume. The tumor included multiple cysts, and the solid portion showed heterogeneous enhancement after the administration of gadolinium (Gd) (Fig. 1B-E). The exact origin of the tumor was indeterminable because the normal anatomic structures were lost. The presumptive diagnosis was a teratoma.

Endoscopic biopsy of the tumor surface in the left lateral ventricle was performed and a ventriculoperitoneal shunt was inserted on the day of admission, resulting in improvement of his activity. Histopathological analysis revealed the proliferation of glial cells, but could not confirm the diagnosis because of the small amount of specimen. The patient's alpha-fetoprotein (AFP) concentration was 3,773.7 ng/ml in serum and 891.3 ng/ml in cerebrospinal fluid (CSF), both of which exceeded the age-related normal range. His serum beta-human chorionic gonadotropin concentration was less than 0.1 ng/ml.

A left-sided craniotomy was performed on hospital day 5, but the operation had to be halted because of a remarkably high vascularity of the tumor. Postoperative MRI of the brain revealed that only 8% of the tumor had been resected. Subsequent histopathological examination revealed a mixture of mature and immature tissues derived from all 3 germ cell layers (Fig. 2A-I). The immature portion was composed of tubular structures that resembled primitive neural tubes (Fig. 2H) and occupied 9% of the total area of the specimen. These histopathological findings confirmed the diagnosis of IMT. Components of other types of GCTs were not present. The Ki-67 labeling index (LI), a proliferation marker, was 95% in tubular structures and 50% in other components (Fig. 2I).

Neoadjuvant chemotherapy using carboplatin (15 mg/kg on day 1) and etoposide (5 mg/kg on days 1-3; CARE regimen) was started on hospital day 12. On follow-up

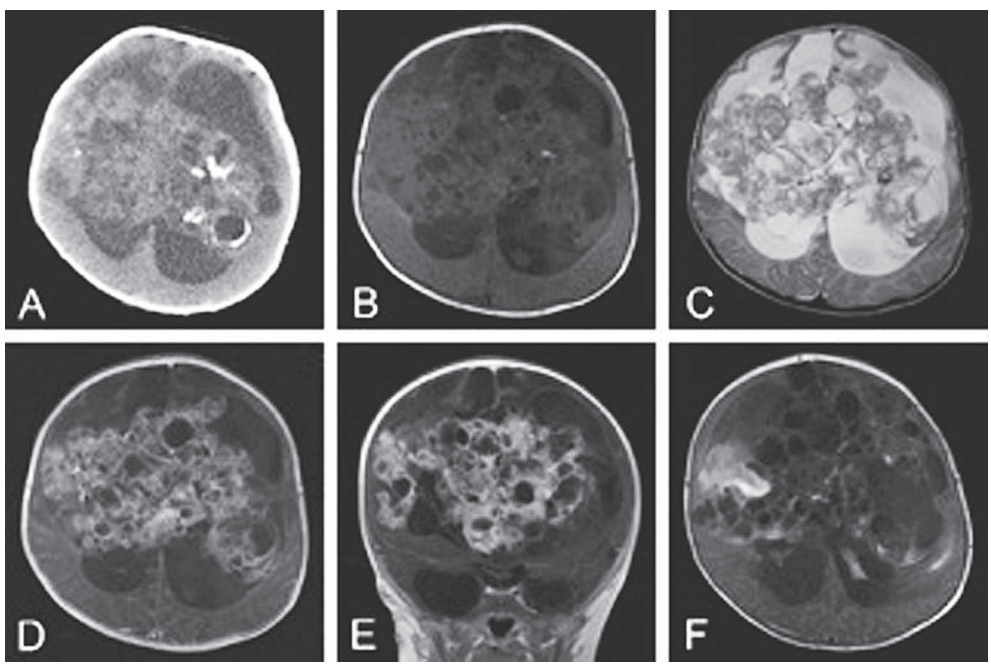

Fig. 1. CT scan and MR images at initial presentation and after chemotherapy initiation.
(A) Axial CT scan showing a large intraventricular tumor containing small calcifications.
(B-E) Axial T1-weighted (B) and T2-weighted (C) MR images showing multiple cysts in the tumor. Axial (D) and coronal (E) Gd-enhanced T1-weighted MR images showing heterogeneous enhancement of the solid portion of the tumor.
(F) Axial Gd-enhanced T1-weighted MR image after the initiation of chemotherapy showing decreased enhancement and slight enlargement of the tumor with postoperative mild intraventricular hemorrhage.
CT, computed tomography; Gd, gadolinium; MR, magnetic resonance.

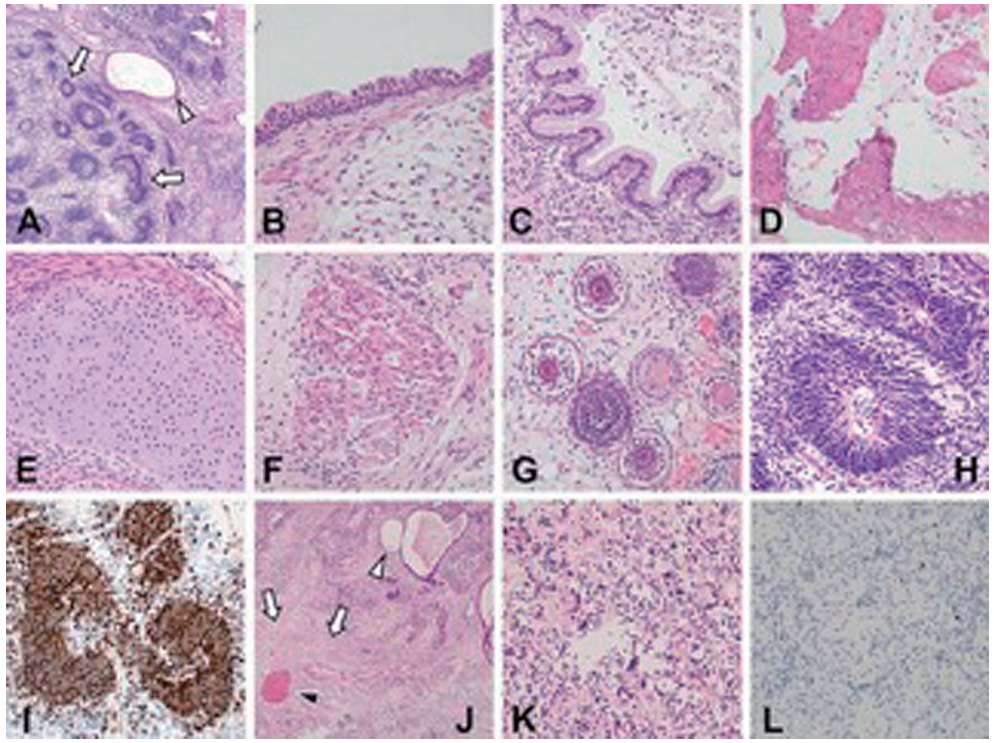

Fig. 2. Photomicrographs of surgical specimens at the first surgical resection and at the last surgical resection.
(A) Photomicrograph showing a mixture of primitive neural tubes (arrow) and mature ciliated bronchial epithelium (arrowhead).
(B-I) Higher magnification images showing ciliated bronchial epithelium (B), intestinal epithelium (C), bone (D), cartilage (E), smooth muscle (F), hair follicle (G), and primitive neural tubes with a high Ki-67 labeling index (H and I).
(J) Photomicrograph showing the appearance of necrosis (arrow) among mature components including ciliated bronchial epithelium (white arrowhead) and striated muscle (black arrowhead).
(K and L) Higher magnification images showing necrosis and a low Ki-67 labeling index.
Hematoxylin & eosin staining (A-H, J and K) and Ki-67 immunohistochemical staining (I and L).
Original magnifications: ×40 (A and J) and ×200 (B-I, K, and L).

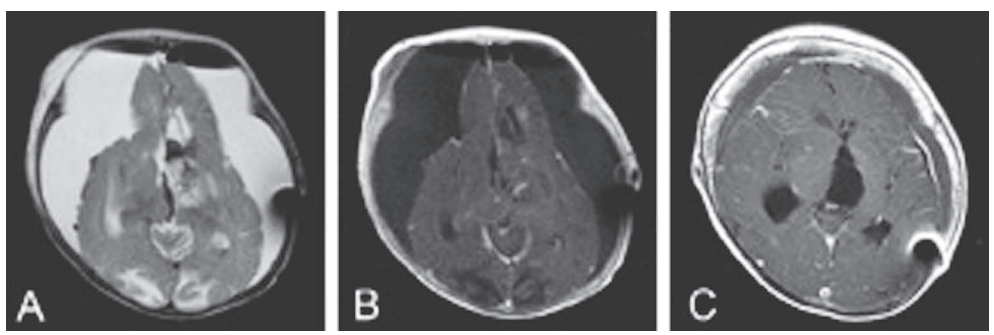

Fig. 3. MR images after the last resection and 3 years after surgery.
(A and B) Axial T2-weighted (A) and Gd-enhanced T1-weighted (B) MR images after the last surgical resection showing the small residual mass without enhancement.
(C) Axial Gd-enhanced T1-weighted MR image 3 years after surgery showing the absence of enhancing lesions.
Gd, gadolinium; MR, magnetic resonance.

MRI of the brain, Gd-enhancement of the tumor appeared to be decreased, but the tumor volume was 16% larger than immediately after the previous craniotomy (Fig. 1F). A second left-sided craniotomy was performed on hospital day 22. The intraoperative findings showed an obvious decrease in tumor vascularity, and a 30% reduction in the tumor size was achieved. A third craniotomy was performed from the right side on hospital day 37, and near-total resection (NTR) was achieved. Postoperative MRI of the brain showed only small residual lesions without Gd-enhancement (Fig. 3A, B). The length of operation time, the calculated volume of intraoperative bleeding, and the extent of tumor resection at each surgical debulking procedure are shown in Table 1.

Table 1. Operation time, intraoperative blood loss, and resected tumor volume at each surgical debulking procedure.

	1st	2nd	3rd
operation time (min)	358	334	536
intraoperative blood loss (% of EBV)	122	29	47
resected tumor volume (%)	8	30	97

$$EBV\ (ml) = BW\ (kg) \times 80\ (ml/kg)$$

$$intraoperative\ blood\ loss\ (ml) = RBC\ (ml) + EBV\ (ml) \times \frac{pre\ Hct - post\ Hct}{pre\ Hct}$$

EBV, estimated total blood volume; BW, body weight; RBC, transfused red blood cells; pre Hct, preoperative hematocrit; post Hct, postoperative hematocrit.

The results of the histopathological analysis at this time were also consistent with a diagnosis of IMT. The percentage of the area occupied by the immature component was 1%. Necrosis appeared and occupied 17% of the total area of the specimen. The Ki-67 LI was 1% (Fig. 2J-L).

His serum and CSF AFP levels decreased after the initiation of CARE chemotherapy and remained within the age-related normal range. The patient underwent 7 cycles of adjuvant CARE chemotherapy and thus, underwent 8 cycles in total. Follow-up MRI of the brain revealed shrinkage of the residual lesions, and the patient has been alive for 3 years after surgery without tumor regrowth (Fig. 3C). He has a delay of neurological development and requires antiepileptic drugs for seizures, but his general condition is stable.

Discussion

Treatment for intracranial teratomas in infants is far from being established. Most previously described cases were congenital tumors and had a very poor prognosis (Larouche et al. 2007). Curative surgical excision has been described in only limited cases with relatively small lesions. Management and treatment outcome of the individual histological subtypes have not been investigated in infants.

Recently, Fukuoka et al. (2014) reported successful treatment of a case of congenital intracranial IMT with neoadjuvant chemotherapy followed by surgical resection. The first attempt at surgical resection failed because of massive intraoperative hemorrhage, and 8 cycles of neoadjuvant CARE chemotherapy was used before the second operation. Neoadjuvant chemotherapy resulted in tumor shrinkage and reduced intraoperative hemorrhage, thus allowing complete resection.

Neoadjuvant chemotherapy is a useful treatment strategy for many types of brain tumors in infants because it decreases tumor volume and vascularity to enable surgical resection. The degree of surgical resection is one of the most important parameters for the survival of infants with brain tumors (Brown et al. 1997; Duffner et al. 1999; Rivera-Luna et al. 2003; Lafay-Cousin and Strother 2009). The ability of neoadjuvant chemotherapy to decrease tumor volume and vascularity was described in infants and young children with brain tumors such as choroid plexus carcinoma (St. Clair et al. 1991-1992; Razzaq and Cohen 1997; Lafay-Cousin et al. 2010; Schneider et al. 2015), choroid plexus papilloma (Addo et al. 2011), medulloblastoma (Di Rocco et al. 1995; Grill et al. 2005), pleomorphic xanthoastrocytoma (Cartmill et al. 2001), primitive neuroectodermal tumor (Razzaq and Cohen 1997; Van Poppel et al. 2011), ependymoma, high-grade glioma, and atypical teratoid/rhabdoid tumor (Van Poppel et al. 2011). However, to our knowledge, only one case report has described this treatment strategy for infantile intracranial teratomas in the literature, even though it is the most common congenital brain tumor with a poor prognosis.

In the present case, maximal surgical resection was first attempted but was unsuccessful because of excessive intraoperative bleeding. Neoadjuvant chemotherapy was then used with the aim of shrinking and devascularizing the tumor. CARE chemotherapy was used because it was an effective neoadjuvant chemotherapy regimen for nongerminomatous GCTs in older children and adults (Kochi et al. 2003; Nakamura et al. 2011). The tumor did not shrink and slightly expanded after the initiation of neoadjuvant chemotherapy, whereas the intraoperative bleeding decreased considerably and NTR was achieved in the subsequent surgery. Even when neoadjuvant chemotherapy does not decrease tumor volume, surgical resection of infantile intracranial IMT should be tried because chemotherapy facilitates surgical resection by reducing tumor vascularity.

In the present case, we used the approximated intraoperative blood loss calculated as the percentage of estimated total blood volume to assess tumor vascularity at each surgical debulking procedure, as reported previously (Schneider et al. 2015). The length of operation time, the volume of intraoperative bleeding, and the extent of tumor resection at each craniotomy are shown in Table 1. Decrease of intraoperative bleeding and the improvement of resected tumor volume after chemotherapy proved the effectiveness of neoadjuvant chemotherapy in the present case.

The surgical specimen at the first craniotomy was obtained from only 8% of the tumor and not from the whole, but comparison of the surgical specimens before and after chemotherapy suggested some histopathological changes. First, the proportion of the specimens occupied by immature tissues decreased after chemotherapy. Immature components accounted for 9% of the total area at the first craniotomy and only 1% at the last craniotomy. Second, tumor necrosis appeared after chemotherapy. Necrosis was absent before chemotherapy, whereas it accounted for 17% of the total area after chemotherapy. These histopathological changes may have been associated with the reduction of tumor vascularity, but the histopathological components of the whole tumor at the first craniotomy could not be investigated, and the mechanism underlying the CARE chemotherapy-induced reduction in tumor vascularity remains unclear.

Intracranial GCTs sometimes paradoxically increase in volume during or after chemotherapy. This phenomenon is called growing teratoma syndrome (GTS) and necessitate surgical excision because the growing mass is a MT and refractory to chemotherapy or radiotherapy. Early detection and early surgical resection is important for GTS (Kim et al. 2011). In the present case, GTS was suspected because the tumor slightly expanded after the initiation of CARE chemotherapy, and the second craniotomy was performed after 1 cycle of chemotherapy. The present case finally did not meet the definition of GTS because immature components did not completely disappear in the surgical specimens after chemotherapy. The possibility of GTS should be noted and early surgical resection should be considered when intracranial IMTs expand during or after neoadjuvant chemotherapy.

We report the use of neoadjuvant chemotherapy as an effective treatment modality for intracranial IMT in an infant. The ability of neoadjuvant chemotherapy to facilitate the surgical resection of intracranial IMTs in infants holds great importance, because this common infantile brain tumor has a dismal prognosis and successful cases have rarely been reported. Our limitation is that we have encountered only 1 case of infantile intracranial IMT. Further investigation is necessary to confirm the role of neoadjuvant chemotherapy in the treatment of intracranial IMTs in infants.

Conflict of Interest

The authors declare no conflict of interest.

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