

Radiotherapy induced intracranial growing teratoma syndrome in a pediatric germ cell tumor: a case report and literature review

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Abstract:

Introduction: Radiotherapy induced intracranial growing teratoma syndrome (iGTS) in a pediatric germ cell tumor (GCT) is a very rare occurrence and so far, only a hand full of authors have observed this correlation. We also observed a case of cogent association between radiotherapy and iGTS.

Case Presentation: We report a case of 4-year-old boy with three months history of headache and projectile vomiting which usually occurred at the early hours of the day. Computer tomographic (CT)-scan of the head showed lateral and third ventricles enlargement which signify hydrocephalus while magnetic resonance imaging (MRI) revealed an enhanced cystic mass around the pineal body. The patient was initially treated with radiotherapy and three months later his symptoms worsened. A follow-up MRI revealed aggressive recurrence of the tumor.

Conclusions: We propose that physicians who choices radiotherapy or chemotherapy do a thorough histological diagnosis prior to commencement of treatment as well as long-term follow-ups.

Keywords: Radiotherapy, Chemotherapy, Teratoma, Intracranial, Hydrocephalous.

Introduction

Primary intracranial germ cell tumors (iGCTs) are rare pediatric tumors with varied geographical occurrences although cases have been reported in adolescents and adult patients. In the East, the occurrence rate is about 0.5-1% while in Asia especially Japan, the occurrence is 2-5%¹⁻⁵. Teratomas on the other hand have incidence rate of about 0.4% as compare to other brain tumors^{6,7}. Intracranial growing teratoma syndrome (iGTS) is a rare complication originating from chemo or radiotherapy and constitutes about 6.5% of all iGCTs^{2,3,7}. This phenomenon was first reported by C. Logothetis et al in 1982 in extracranial GCTs^{3,8}. Intracranial GCTs and extracranial GCTs have similar histologic, genetic, and therapeutic characteristics⁹.

Interestingly, the tumor location and size usually influences the clinical features of iGCTs⁹. The pineal and chiasmatic-sellar areas which are often referred to as the neurohypophysis are the most frequent location^{4,5,9}. Therefore, endocrine abnormalities, increased intracranial pressure (ICP), and visual changes are the main clinical presentation^{3,9}. GCTs are classified into germinomas and non-germinomatous germ cell tumors (NGGCTs) base on three (3) fundamental criteria. The control of initial elevated tumor markers such as alpha fetoprotein (α -AFP) and/or beta-human chorionic gonadotropin (β -HCG), upsurge of tumor size during or after chemo or radiotherapy, and absence of any NGGCT component, other than mature teratoma, in the pathologic examination^{2,10}. The NGGCT comprise of mature and immature teratoma, teratoma with malignant transformation, embryonal carcinoma, yolk sac tumor, and choriocarcinoma^{2,10}. Very few authors have reported cases of radiology induced iGTS although the initial association was with chemotherapy. We present another case of radiotherapy induced

iGTS in a pediatric germ cell tumor and review the possible course of this rare occurrence.

Case report

We report a case of 4-year-old male child who presented with three months history of headache and projectile vomiting at of our facility (West China Hospital). The headache, nausea and vomiting were usually severe in the early hours of the day. The vomiting was three times a day and not associates with visual disturbances, hearing loss, tinnitus, limbs twitching or seizures, as well as incontinence. He was first seen at the local hospital where they treated him as a case of viral encephalitis and his condition improved and he was discharged home five days prior to presentation at our facility (West China Hospital). His immunization was completed according to his age. He had a past medical history of hydrocelectomy on account of hydrocele with no history of head trauma. The parents denied exposure to external radiation of any kind. Physical examinations as well as neurological examinations were unremarkable.

CT of the head showed lateral and third ventricles significantly enlarged signifying hydrocephalus. MRI of the head also revealed an enhanced cystic mass around the pineal body which was hypo-dense on T1, hyper-intense on T1 and on FLAIR the mass was more hypo-intense than the cerebrospinal fluid (CSF) measuring about 1 x 1 x 1 cm (**Figure 1, A-C**). Routine laboratory investigations were essentially normal. Tumor biomarkers are as shown; α -AFP: 8.69 ng / ml, β -HCG: 0.24 mIU / ml. A working diagnosis of germ cell tumors was made. After taking the parents through a series of education and counseling sessions, they opted for radiotherapy. Whole ventricular radiation dose of 23.40 Gy fractionated 13 times with 1.80 Gy per time was delivered and a ventriculostomy

done. The patient was discharged home and scheduled visits arranged every three months.

The goal of the scheduled visits was to monitor the progress of the tumor with routine MRI after the radiotherapy. During the first three months scheduled visit, the patient still complains of severe headaches as well as early morning projectile vomiting. MRI done revealed an increase in size of the cystic mass in the third ventricle which is hypo-intense on T1, hyper-intense T2 and on FLAIR hypo-intense. The lesion was enhanced, nodular and this time measuring about 3.5x2.6x2.4 cm (**Figure 1, D-F**). After taking the parents through another series of education and counseling session, the patient was admitted in the neurosurgery ward and surgery scheduled the next day. Using the anterior interhemispheric transsplenic approach, the lesion was totally resected. Intraoperatively, the lesion was seen with irregular texture, rich blood supply and clear boundaries. Pathological examination revealed cyst-like lesion, lined with monolayer or squamous epithelium or intestinal epithelium with scattered hair follicles, sebaceous glands as well as adipose tissue (**Figure 2**). These findings are in line with mature cystic teratoma.

Discussion

Intracranial growing teratoma syndrome (iGTS) is very rare and a very few authors have described this phenomenon with only single cases^{3,10}. This phenomenon was initially seen in iGCT patients receiving only chemotherapy⁷ and later also observed in iGCT patients who have radiotherapy too^{3,10}. Teratomas are made up of about 0.5% of all intracranial tumors and ten-year survival of patients with mature and immature teratomas is 90 and 70%, respectively. Most patients with malignant transformation of teratoma demonstrate poorer survival of less than 50%^{6,11}. Intracranial GCTs frequently

occur in children and adolescents with sporadic case in adults. Virtually 90% of cases occurs before the age of 20 years with peak incidence between 10-12 years of age. Interestingly, 70% of tumors occurrence in males and are usually located at the pineal region while 75% of tumors occurrence in females and are usually located at the suprasellar area^{9,12}. Intracranial GCTs can occur as a solitary nodule or multiple lesions. Anatomically, the ratio of pineal area lesions to suprasellar area is about 2:1 although approximately 5-10% of patients have lesions involving both suprasellar and pineal gland at the time of diagnosis⁹. Lesions associated with these two areas are referred to as the so-called "doublet lesions" and they are usually pure germinomas^{9,12}.

The etiology of the iGTS is still a matter of debate although chemotherapy⁷ and radiotherapy^{3,10} forms an essential hypothetically part in the etiology of this syndrome. The most proposed potential origins of this syndrome revolve around three (3) characteristics. Firstly, chemotherapy and radiotherapy destroy only the cancer cells leaving mature benign elements. Secondly, chemotherapy or radiotherapy trigger modifications in the kinetics of cells and transformation of a malignant tumor into a benign mature teratoma and thirdly, the Hong et al. hypothesis which states that malignant cells differentiate into benign cells under the stimulus of chemotherapy or radiotherapy^{2,3,10,13}. Therefore, the susceptibility of iGTS to any therapy modality will depend on firstly understanding of this phenomenon above; secondly, detailed diagnostic evaluation of patients with iGCTs when the patient is subjected to chemotherapy or radiotherapy; thirdly, early recognition of the paradoxical reaction of the tumor to chemotherapy or radiotherapy that is growing of the tumor into a larger size and the normalization of tumor markers in the

blood; and fourthly, total resection of the tumor.

The primary clinical manifestation of iGCTs reliant on the patient's age, tumor location, and tumor size. Pineal area lesions typically show signs of ICP due to obstructive hydrocephalus and frequently necessitating shunt placement or ventriculostomy. Other signs include ophthalmologic abnormalities, somnolence, ataxia, seizures, and behavioral changes. Endocrinopathies, disorders of sex development (DSD) and diabetes insipidus (DI) have also been associated with pineal area lesions. Parinaud's syndrome, occurring as a result of the association of adjacent midbrain structures has also been reported in 50% of pineal GCTs^{9,14,15}. On the other hand, suprasellar GCTs commonly show signs of hypothalamic/pituitary axis dysfunction such as DI, delayed sexual development, hypopituitarism, isolated growth hormone deficiency, and precocious puberty. Furthermore, some patients may also show signs of ophthalmic abnormalities such as bilateral temporal hemianopsia. Patients with suprasellar GCTs rarely show signs of increased ICP and some may even be asymptomatic for 6 months prior to diagnosis. The asymptomatic cases are usually seen with undiagnosed isolated endocrinopathies^{9,14,15}.

A part from the clinical symptoms and signs above, tumor markers (α -FTP and β -HCG), neuroimaging characteristics, and cytological (CSF) and/or histological assessments are crucial in the diagnosis and follow-up of patients⁹. The verification of diagnosis entails quantity of serum and CSF tumor markers (α -FTP and β -HCG) and/or biopsy⁹. Radiographic features of iGCTs alone are does not dependably distinguish germinoma from NGGCTs or other tumors at this location⁹. CT-scan and MRI are extremely sensitive in revealing suprasellar and pineal area masses although the

radiographic features are extremely alike in all iGCTs. Consequently, the diagnosis of GCTs should encompass contrasted and uncontrasted MRI and measurement of tumor markers (α -FTP and β -HCG) levels in blood as well as CSF⁹.

Although a combination of Cisplatin and Etoposide have produced satisfactory abrupt outcomes (80%) as chemotherapy in iGCTs, Cisplatin alone is very effective in management of malignant situations^{11,16}. With respect to chemotherapy, the iGTS is noted to progress typically in patients with mixed GCTs and immature teratoma^{2,7}. Furthermore, in aligned with advancing tumor's size even with combined chemotherapy surgeons predominantly notice progressive tumor growth. Our case above is not different since the radiation induced iGTS occurred three months after the initiation of therapy. We are therefore of the view that both radiotherapy and chemotherapy induce iGTS approximately the same time frame.

Maria et al in their review on iGCT indicated that iGCTs are extremely susceptible to radiation therapy and in majority of patients, total response can be realized with radiotherapy alone⁹. Although reports have indicated that radiotherapy alone have achieved five-year survival rates of 90%, the ideal doses and fields of radiation is still a matter of debate. The high survival rate above therefore, has prompted most physicians to concentrate on the reduction of concentration of radiation in an attempt to decrease late adverse reaction of radiotherapy^{6,9,11}. Furthermore, although no clear standard treatment guidelines for iGCTs exist, most physicians start with at least 50 Gy to the site of the lesion and then top-up with prophylactic therapy to the craniospinal axis. They however disregard the adverse effects of these huge volumes and high doses though some multiple research has delivered low doses of radiation

at main site of lesions with a sustained treatment rate 90%^{9,17-20}. In view of the arguments put forward by Maria et al, several authors^{3,10} including us with single cases have observed a strong correlation between radiotherapy and aggressive recurrence of iGCTs.

Khoo et al with an adult case who they treated with 50 Gy/28 fractions of whole brain radiation therapy noted a tally decrease in size of the mass and their patient achieved a tremendous recovery with absolute resolution of his condition. They indicated that a five years radiological follow-ups of their case revealed no signs of advancement of his lesion which means that adult patients benefit more with radiology therapy than their pediatric counterparts¹. The precise clinical pattern of β -HCG-secreting iGCTs is still very controversial, and in numerous situations, patients with β HCG-secreting GCTs seem to have poorer outcomes with the use of irradiation alone^{9,11}. The reduction of tumor marker (α -FTP and β -HCG) levels in the blood and paradoxical increase in the size of the tumor with chemotherapy alone or radiology alone and/or both and verified histological diagnosis of mature teratoma after resection of the tumor usually demonstrate the GTS^{3,10}. Our patient had very low β -HCG secretion that could result in the induction of the teratoma syndrome. We therefore propose the induction of iGTS could be as a result of low levels α FTP and β HCG during the treatment with radiotherapy or chemotherapy. Also, very low levels of these hormones could be a good prognostic tool. It could also mean that these hormones may not be responsible for the aggressive recurrence of the tumors so we propose further studies with both animal and human models will be beneficial.

The therapy for iGTS should include surgical resection of the lesions and patients with signs and symptoms of obstructive

hydrocephalus have placement of either a VPS or an endoscopic third ventriculostomy (ETV)^{9,10}. Most authors are of the view that radiotherapy is not necessary after total resection of the tumor and when metastases are nonexistent^{2,7}. The existence of tumor remnants and/or metastases after partial resection has a poor prognosis because the growing residual tumor usually have mature teratoma on histologic examination and hence unresponsive to either radiation therapy or chemotherapy².

Conclusions

We are highly in favor of phenomenon that radiotherapy can induce the iGTS. The dose and fraction of radiotherapy does not matter in the induction of iGTS but the present of β HCG-secretion is the main determiner. The gold standard for the treatment of iGCTs so far is total tumor resection with placement of either a VPS or an ETV. We propose that physicians who consider radiotherapy or chemotherapy options should do a thorough histological diagnosis prior to commencing treatment as well as long-term follow-ups.

DECLARATION

Ethics approval and consent to participate:

The ethical committee of West China Hospital full approved our case study. The child's parents were informed about our intension to involve him in a case study and they agreed to partake in the study. They signed the concern form before the operation was carried out according to all surgical protocols.

Consent for Publication:

The child's parents were dually informed about our intention to publish his case and they fully concerted to the use of these documents. The hospital also

concerted to the use of this information for publication.

Authors' contributions:

S.A.R and S.P conceived the project and S.A.R designed the study. S.A.R, S.P and Y.F collected patient's data. Y.J and C.Y provided technical assistance in the study. S.A.R and S.P prepared the illustrations. S.A.R and S.P analyzed data and **S.A.R wrote the paper**. All authors approved the paper for the submission.

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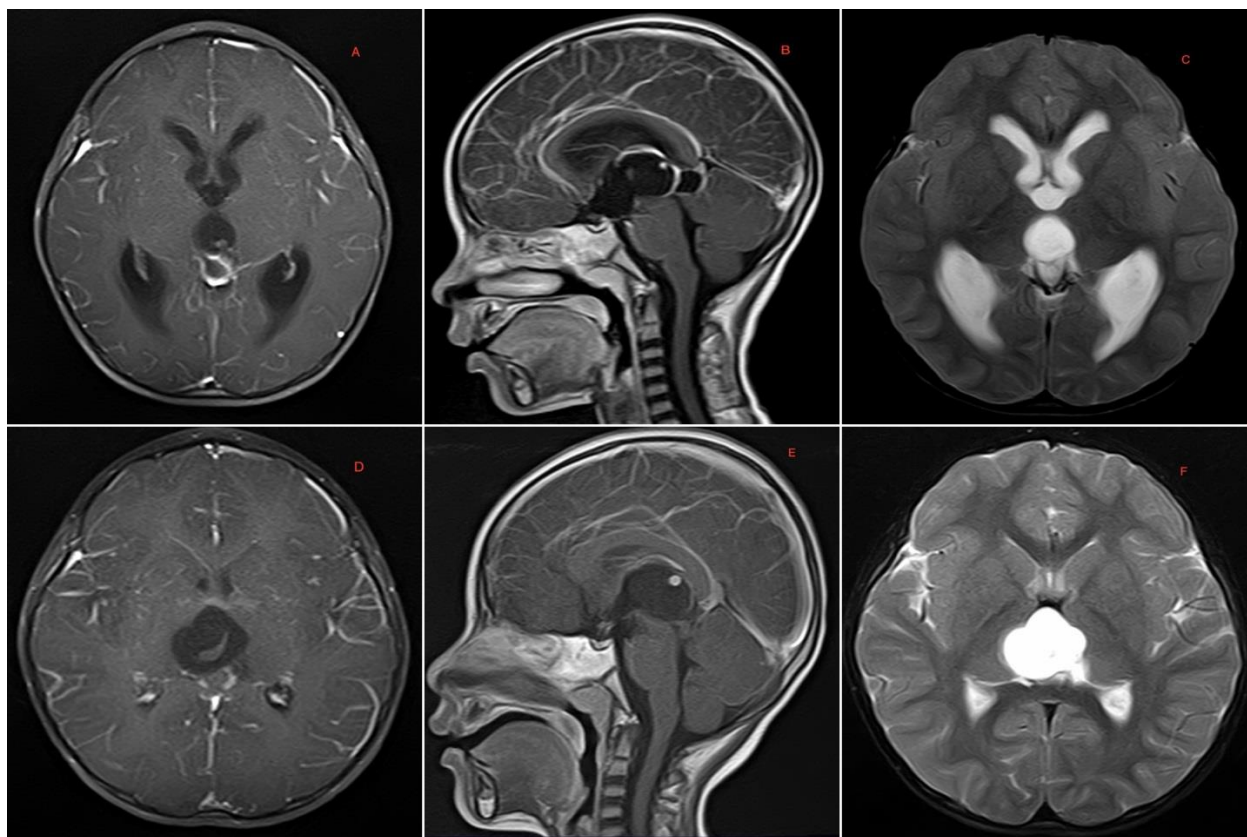


Figure 1. A: axial T1, B-sagittal T1 & C-axial T2 images showing the tetratoma before radiotherapy. D: axial T1, E: sagittal T1 & F-axial T2 images showing significant enlargement of the tetratoma three weeks after radiotherapy.

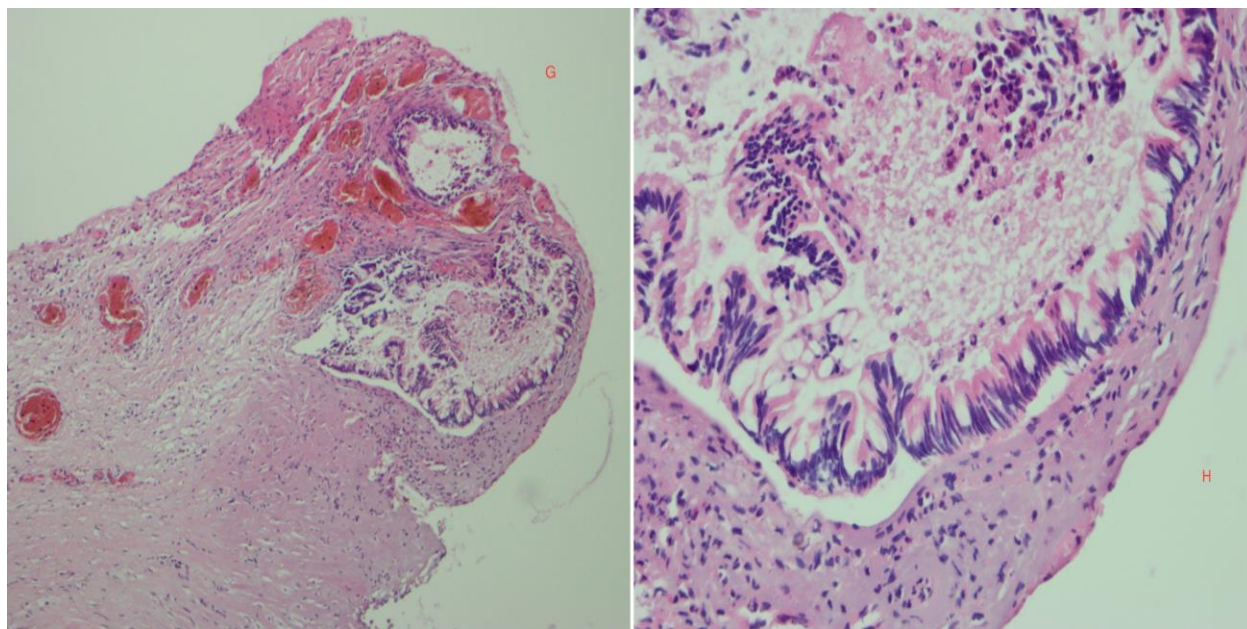


Figure 2. Are histopathology images of the tetratoma showing cyst-like lesion, lined with monolayer or squamous epithelium or intestinal epithelium with scattered hair follicle, sebaceous glands as well as adipose tissue.