Original Article

Primary intracranial germ cell tumors: A single institution experience from a South Indian Tertiary Cancer Center

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ABSTRACT

Background: Intracranial germ cell tumors (ICGCTs) are rare tumors seen in the pineal and suprasellar regions. The World Health Organization has classified ICGCTs into germinoma and nongerminomatous GCT (NGGCT). Germinoma is radiosensitive and has excellent survival rate. Patients with NGGCTs are less sensitive to radiotherapy and have less favorable outcome. **Objective:** This retrospective observational study was carried out to determine the clinical features, treatment, and outcome of patients diagnosed as ICGCT from June 2006 to June 2014. **Materials and Methods:** Patients' medical records were reviewed for information regarding age, gender, presenting features, treatment instituted, complications, and treatment outcome. **Results:** Seven patients with ICGCT were studied. Their age ranged from 4 to 24 years, with median age being 13 years. All of them were male. Four patients had germinoma and three had mixed NGGCT. Four patients had pineal region mass, two patients had suprasellar mass, and one patient had bifocal disease with both pineal and suprasellar involvements. Following surgical debulking or ventriculoperitoneal shunt, patients received radiation and chemotherapy. One patient of germinoma and another patient of NGGCT died due to febrile neutropenia/sepsis. The overall survival was 4 years for patients with both germinoma and NGGCT. **Conclusions:** ICGCTs are rare tumors seen in the second decade of life, with male preponderance. With judicious use of chemotherapy and radiotherapy, germinoma has excellent survival outcome. The outcome of NGGCT can be improved with multimodality treatment.

Key words: Alpha-fetoprotein, blood–brain barrier, cerebrospinal fluid, intracranial germ cell tumors, lactate dehydrogenase, nongerminomatous germ cell tumor, β human chorionic gonadotropin

INTRODUCTION

Intracranial germ cell tumors (ICGCTs) are rare tumors that account for 2–3% of all primary brain tumors in children.[1,2] Ninety percent of the cases of ICGCT occur before 20 years of age.[3,4] Incidence of ICGCT is higher in Japan and Asia compared to Western countries and accounts for nearly 11% of pediatric brain tumors.[5] ICGCT arises in midline structures usually in the pineal and/or suprasellar regions of the brain, either as solitary or multiple lesions. The World Health Organization has classified ICGCTs into germinoma and nongerminomatous GCT (NGGCT).[6] NGGCT include choriocarcinoma, embryonal carcinoma, yolk sac tumor, teratoma and mixed GCT. Germinoma is radiosensitive and has excellent survival rate. Patients with NGGCTs are less sensitive to radiotherapy and have less favorable outcome. This retrospective study was undertaken to

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Access this article online

Quick Response Code:

Website: www.ccij-online.org

DOI: 10.4103/2278-0513.186099

Cite this article as: Dasappa L, Babu G, Chennagiriyappa LK, Appaji L, Pramod K, Amirtham U, *et al.* Primary intracranial germ cell tumors: A single institution experience from a South Indian tertiary cancer center. Clin Cancer Investig J 2016;5:299-304.

describe the clinical features and management of patients diagnosed as ICGCT at our institute.

MATERIALS AND METHODS

This was a retrospective observational study carried out to determine the clinical features, treatment details, and outcome analysis of patients diagnosed as ICGCT from June 2006 to June 2014. Patients' medical records were reviewed for information regarding age and gender, presenting features and site of involvement, treatment protocol, response to therapy, complications during treatment, and treatment outcome. Diagnosis of ICGCT relied either on histopathology of surgical specimen or on a stereotactic biopsy or cerebrospinal fluid (CSF) tumor markers or both. If biopsy was not feasible, diagnosis was based on CSF tumor markers and radiological findings. Patient was considered to have germinoma if he/she has one of the following (as used in the COG-ACNS1123 (NCT01602666) trial):

- Either pineal region tumor or suprasellar primary tumor, normal alpha-fetoprotein (AFP) level and β human chorionic gonadotropin (β HCG) level between 5 and 50 mIU/ml in serum and/or CSF
- Bifocal presentation (pineal and suprasellar), diabetes insipidus, normal AFP level and β HCG level lower than 100 mIU/ml in CSF.

Complete workup of patients included complete blood count, complete metabolic profile, serum tumor markers (AFP, β HCG, lactate dehydrogenase [LDH]), CSF tumor markers (AFP, β HCG, LDH), CSF cytology, magnetic resonance imaging of the brain and spine, and glomerular filtration rate scan. CSF tumor markers were considered elevated if CSF AFP >50 ng/ml and β HCG >100 mIU/ml.

Stage was assigned according to modified Chang staging system:[7] M_0 - localized disease with CSF cytology negative; M_1 - CSF positive cytology only; M_2 - gross nodular seeding in cerebellar-cerebral subarachnoid space and/or lateral or third ventricle; M_3 - gross nodular seeding in spinal subarachnoid space; M_4 - extraneural metastasis.

RESULTS

During the study period, seven patients with ICGCT were treated at our institute. Their age ranged from 4 to 24 years, with median age being 13 years. All the patients were male. Four patients had germinoma [Table 1] and three had NGGCT [Table 2] histology. Four patients had histopathological diagnosis whereas three were diagnosed based on radiological features and CSF tumor markers only. Four patients had pineal region mass [Figures 1 and 2], two patients had suprasellar mass, and one patient had bifocal disease with both pineal and suprasellar involvements. Headache was the most common presenting complaint seen in six patients. Four patients had cranial nerve palsies. Three patients had visual disturbances such as double vision and loss of vision. One patient had hemiparesis and another patient had precocious puberty. All four patients of germinoma had normal CSF tumor markers. Two patients of NGGCT had elevated AFP ± elevated β HCG, and one patient of NGGCT had elevation of β HCG alone. Three patients with germinoma had localized disease without CSF involvement (M_0) and one patient had CSF cytology positive (M_1). All of the patients with NGGCT had CSF involvement (M_1). None of our patients in the series had cerebral, cerebellar, or spinal seeding or extracranial metastases (M_2/M_3/M_4). None of the patients had serum tumor markers elevated.

Primary surgical excision/debulking was done in three patients whereas the remaining four underwent ventriculoperitoneal (VP) shunting for management of raised intracranial pressure and hydrocephalus. Following surgical debulking or VP shunt, all patients of seminoma

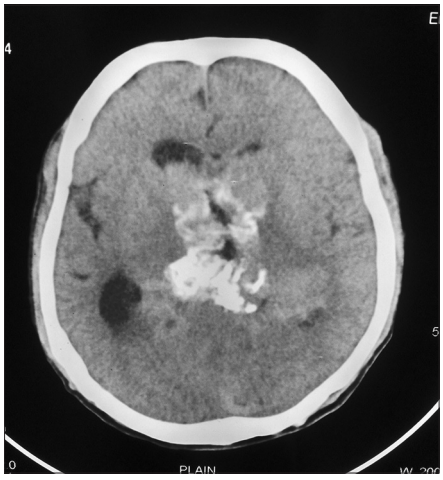

Figure 1: Computed tomography of the brain showing intracerebral calcification

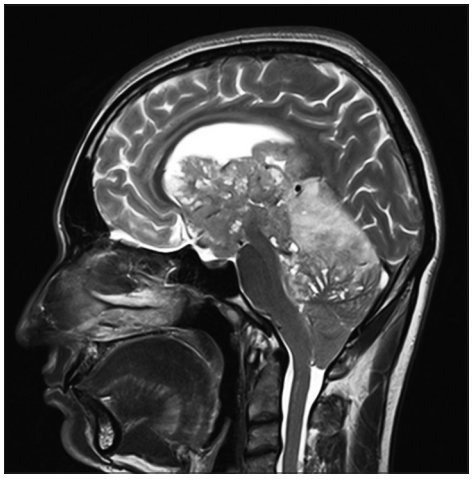

Figure 2: Magnetic resonance imaging of the brain showing a pineal mass

Table 1: Clinicopathological features and management of patients with germinoma

Age (in years)	Sex	Presentation	Imaging	Histopathology	CSF markers			CSF cytology	Staging	Primary treatment	Adjuvant treatment	Follow-up
					AFP	β HCG	LDH					
4	Male	Headache, vomiting, loss of vision	Suprasellar mass 3 cm × 3 cm × 2 cm extending up to caudate nucleus	Germinoma	0.99	0.10	190	-	M_0	Right temporal craniotomy and decompression	EBRT 45Gy/25# followed by 3 cycles BEP	Follow-up 8.5 years, asymptomatic
13	Male	Headache, vomiting, Parinaud syndrome	Pineal region mass 3.2 cm × 4.1 cm × 3.7 cm, another lesion in suprasellar region involving optic chiasm 1.5 cm × 1.1 cm × 2 cm (bifocal)	No	0.6	43.07	220	+	M_1	VP shunting	IMRT 36Gy/20# to brain and 36Gy/20# to spine followed by 3 cycles BEP	Patient died following 3rd cycle of BEP due to febrile neutropenia/ sepsis
15	Male	Double vision, giddiness	Lesion in pineal region 2.3 cm × 2.5 cm with hydrocephalus	Germinoma	1.5	0.1	244	-	M_0	VP shunting and subtotal decompression	EBRT 45Gy/25# followed by 3# BEP	Follow-up 3 years, impaired hearing, MRI no residual disease
17	Male	Headache, gait ataxia, bilateral 6th nerve palsy	Pineal mass 2.9 cm × 2.4 cm with obstructive hydrocephalus	Germinoma	2.14	7.05	198	-	M_0	VP shunting and stereotactic biopsy	IMRT 45Gy/25# followed by 4 cycles EP	Follow-up 5 years asymptomatic, CT brain no residual/ recurrent disease

#Fraction, +: Positive cytology, CSF: Cerebrospinal fluid, AFP: Alpha-fetoprotein, β HCG: β human chorionic gonadotropin, LDH: Lactate dehydrogenase, VP: Ventriculoperitoneal, EBRT: External beam radiotherapy, BEP: Bleomycin, etoposide, cisplatin, EP: Etoposide, cisplatin, MRI: Magnetic resonance imaging, CT: Computed tomography, IMRT: Intensity-modulated radiation therapy

Table 2: Clinicopathological features and management of patients with nongerminomatous intracranial germ cell tumors

Age (in years)	Sex	Presentation	Imaging	Type of GCT	Histopathology	CSF markers			CSF cytology	Staging	Primary treatment	Adjuvant treatment	Follow-up
						AFP	β HCG	LDH					
8	Male	Headache, precocious puberty, 3rd and 6th cranial nerve palsy, nystagmus	Mass in the third ventricle 3.7 cm × 2.8 cm with midbrain compression and hydrocephalus	Mixed NSGCT	No	74.6	929	198	+	M_1	VP shunting	EBRT 50Gy/25# to primary and 36Gy/18# to spine followed by 5 cycles BEP	Residual lesion present, follow-up 6 years, MRI stable disease
13	Male	Headache, hemiparesis, facial palsy, bilateral papilledema	Suprasellar lesion 2.5 cm × 4 cm × 2.1 cm	Mixed NSGCT	Mixed GCT immature teratoma, endodermal sinus tumor	110	0.1	225	+	M_1	Right frontal craniotomy and decompression	4 cycles BEP followed by EBRT 45Gy/30# to primary and 36Gy/18# to spine	Follow-up 4 years, asymptomatic, CT brain no residual/ recurrent disease
24	Male	Headache, double vision, bilateral 6th cranial nerve palsy and upward gaze palsy	Pineal region mass 6 cm × 4 cm × 6.9 cm [Figures 1 and 2]	Mixed NSGCT	No	5.01	334.4	200	+	M_1	VP shunting	Completed 2 cycles of BEP	Patient died due to febrile neutropenia and sepsis following second cycle of chemotherapy

#Fraction, +: Positive cytology, NSGCT: Nervous system germ cell tumors, GCT: Germ cell tumors, CSF: Cerebrospinal fluid, AFP: Alpha-fetoprotein, β HCG: β human chorionic gonadotropin, LDH: Lactate dehydrogenase, VP: Ventriculoperitoneal, EBRT: External beam radiotherapy, BEP: Bleomycin, etoposide, cisplatin, EP: Etoposide, cisplatin, MRI: Magnetic resonance imaging, CT: Computed tomography, IMRT: Intensity-modulated radiation therapy

received cranial/craniospinal irradiation followed by chemotherapy (either three cycles of bleomycin, etoposide, cisplatin or four cycles of etoposide, cisplatin). One patient of germinoma died following the last cycle of chemotherapy

due to febrile neutropenia/sepsis. Patients with germinoma had a median overall survival of 4 years. Among patients with NGGCT, one patient received neoadjuvant chemotherapy followed by craniospinal irradiation and another patient died due to febrile neutropenia following neoadjuvant chemotherapy. One patient received cranial irradiation followed by chemotherapy. Patients of NGGCT had a median overall survival of 4 years. All the surviving patients are disease-free and have excellent neurological and scholastic performance.

DISCUSSION

Primary ICGCTs are rare and share histologic, genetic, and therapeutic similarities to extracranial GCTs. The pathogenesis of ICGCT is unknown. The germ cell theory proposes that primordial germ cells aberrantly migrate to the central nervous system (CNS) and undergo malignant transformation.[8,9] The embryonic cell theory proposes that pluripotent embryonic cell aberrantly migrates and progresses to ICGCT.[2,5]

The reported incidence of ICGCT is significantly higher in Asian countries compared with Western countries.[10] Ninety percent of ICGCTs occur in patients before the age of 20 years.[5] The peak incidence for ICGCTs is 10–12 years of age.[5] Males have higher incidence of CNS GCTs than females, starting in the second decade.[3] The reported rate of pineal region ICGCT is higher in Asia where it exceeds 9% of all intracranial masses.[11] Our study results are consistent with previously published literature, with median age of 14 years, male preponderance, and higher incidence of pineal involvement. NGGCTs occur more commonly in younger children, whereas pure germinomas are more commonly seen in older patients.[5] In our series, median age of patients with germinoma was 14 years and that of NGGCT was 13 years.

Clinical presentation consists of ocular signs or signs of obstructive hydrocephalus. The anatomic relationship between the pineal gland and the quadrigeminal plate, third ventricle, and deep venous structures accounts for most of the symptoms associated with pineal region tumors. Major symptoms are headache, nausea, vomiting, lethargy, and visual disturbances. Ocular signs predominate and include upward gaze, papillary abnormalities, and papilledema.[11] Ataxia, hemiparesis, and brain stem hemiatrophy may also be present.[12,13] Other symptoms at diagnosis may include weight loss, diabetes insipidus, amenorrhea, retardation, and precocious puberty. NGGCT tends to present with larger tumors and more severe neurologic compromise at the time of diagnosis, including a higher incidence of hydrocephalus and visual dysfunction.

Germinomas account for approximately 50–70% of cases and NGGCTs make up the remaining third. In a series of 176 ICGCTs studied by Wong *et al*., in Taiwan, 58.5% were germinomas and 41.5% were nongerminomas.[14] In our series, four patients had germinoma and three had NGGCT. Elevations of tumor markers along with imaging findings are used as surrogate diagnostic markers for ICGCT and may obviate the need for histological diagnosis.[15]

CSF tumor markers can also be used to monitor response to treatment.[11] Some studies indicate that patients with elevated serum and/or CSF markers have a poorer overall survival.[16] If reassessment suggests increasing tumor size but CSF tumor markers have normalized with treatment, growing teratoma syndrome should be considered and surgical resection should be planned.

ICGCTs have demonstrated sensitivity to chemotherapy and radiation similar to gonadal and extragonadal GCT. Germinomas are highly radiosensitive whereas NGGCT is less sensitive to radiation. Prognosis and management protocol of ICGCT depend on histology.[11] Although germinomas are curable with cranial or craniospinal irradiation alone, use of neoadjuvant chemotherapy allows reduced dose and volume of radiation. This might reduce the long-term radiation therapy-related adverse neurocognitive effects. NGGCTs are treated with neoadjuvant chemotherapy followed by craniospinal irradiation with improved survival rates. Mature teratomas are treated with surgery alone.

The effectiveness of different systemically administered chemotherapy for brain tumors is dependent on whether the active drugs can cross the blood–brain barrier (BBB). Chemotherapeutic agents which fail to penetrate the intact BBB enter the brain when that barrier has been disrupted, as by the presence of aberrant tumor vascularity, prior brain irradiation, or surgery.[17-19] In addition, the pineal body is one of the non-BBB regions in the brain, favoring usefulness of chemotherapy.[20] Chemotherapeutic agents used in germinomas include cisplatin, carboplatin, etoposide, cyclophosphamide, and ifosfamide in different combinations. NGGCTs are treated with different combinations of agents such as cisplatin, carboplatin, etoposide, bleomycin, ifosfamide, and vinblastine. The specific chemotherapy regimen and length of therapy are under investigation. The role of intrathecal methotrexate in the management of ICGCT is not sure with many investigators used it in the past. None of our patients received intrathecal methotrexate.

Notable finding in our series was two deaths associated with febrile neutropenia following chemotherapy. In patients with GCT, it is important to maintain the dose intensity of chemotherapy with the aid of hematopoietic growth factors and prophylactic antibiotics as indicated,

and treatment-related mortality is avoidable with the use of intensive supportive care. This case series underscores the importance of improvement of supportive care measures in oncology in improving clinical outcome in patients in developing nations.

The optimal radiation field, timing, and dose are also under investigation. Doses of primary site irradiation in most series have ranged between 4000 and 5500 cGy.[21,22] CSF dissemination (M1) requires craniospinal irradiation. In a review of forty patients, treatment with 5200 cGy of local irradiation therapy, 3240 cGy of whole brain irradiation therapy, and 2600 cGy spinal radiation therapy resulted in a 5-year, progression-free survival rate of 97% in patients who had evidence of leptomeningeal disease at the time of diagnosis as long as craniospinal irradiation was given.[23]

The prognosis for GCTs, independent of their location in the CNS, is highly dependent on the histological subtype of the tumor present. In reported series of patients treated for GCTs, it is often difficult to determine the relative prognosis of a specific type of tumor, given the variability of treatment, even at one institution. In general, germinomas carry an excellent prognosis, with most series suggesting 5-year progression-free survival rates and cure in well over 90% of patients.[24] In contrast, NGGCTs, including mixed GCTs and embryonal cell carcinomas or tumors that have been termed yolk sac tumors, have a poorer prognosis, with reported survival rates ranging between 40% and 70%.[25,26] Recent reports have suggested a better outcome for NGGCTs, especially mixed GCTs, with the use of more aggressive multimodality therapy.[27,28]

High-dose chemotherapy with autologous stem cell rescue has shown promise as consolidation therapy for some high-risk GCTs. In an attempt to avoid radiotherapy by using high-dose chemotherapy, six patients were treated following gross total excision of their tumor with four to seven courses of high-dose cisplatin (200 mg/m^2), etoposide (1250 mg/m^2), and ACNU (150 mg/m^2), followed by autologous stem cell rescue. All patients were alive and living with good performance status 1–7 years following diagnosis.[29] With multimodality treatment, patients in our series had an excellent survival.

The limitation of this study is the small number of patients, the heterogeneity in terms of chemotherapy protocols and radiation dose, fractionation, and field. This heterogeneity makes it impossible to make generalization of our results.

CONCLUSIONS

ICGCTs are rare intracranial tumors seen in the second decade of life, with male preponderance. Pineal tumors are more common in Asians, and germinoma is more common compared to NGGCT. Diagnosis of ICGCT can be made with or without histopathological examination if neuroimaging and CSF tumor markers are suggestive. With judicious use of chemotherapy and radiotherapy, germinoma has excellent survival outcome. The outcome of NGGCT can be improved with multimodality treatment.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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