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Original Investigation

Primary Intracranial Germinomas: Retrospective Analysis of Five Cases

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ABSTRACT

AIM: Primary intracranial germinomas (PIGs) are rare malignant brain tumors that represent approximately 0.2% to 1.7% of all primary intracranial tumors. PIGs have infrequent, but there is a possibility of spinal cord metastases. In this study, clinical outcomes of five consecutive PIGs have been presented.

MATERIAL and METHODS: Medical records were retrospectively reviewed in 1,849 cases of intracranial tumors who underwent surgery between the years 2005 and 2015 and cases confirmed as germinoma histopathologically were included in this study.

RESULTS: Five cases of PIGs were detected in two female (40%) and 3 male (60%) patients. The mean age was 15.2±5.6 (8-23) years. The mean follow-up period was 52.3±56.4 (9-135) months. The most common complaint was headache (60%), followed by nausea±vomiting (40%). Four cases (80%) affected the suprasellar region while the fifth patient's tumor was localized in the pineal region. The duration between the initial symptom and time of surgical intervention ranged between 15 days and 2 months. Twelve months after the first operation, one patient presented with drop seeding metastasis. Four-year survival (with exception of the case that died as a early surgical complication) was 100%. Gross total resection (GTR) was achieved in one patient. Surgical mortality rate was 20%. PIGs' morbidity rate was 60%.

CONCLUSION: PIG is a mostly malignant tumor that generally affects the pediatric age group. They are radiosensitive tumors. Subtotal or near-total using stereotactic guide or direct surgery to confirm the histopathological diagnosis followed by chemotherapy and whole brain or in some cases craniospinal radiotherapy rather than GTR is therefore the treatment of choice.

KEYWORDS: Primary intracranial germinoma, Pineal gland, Suprasellar region, Radiotherapy, Drop metastasis

INTRODUCTION

Primary intracranial germinomas (PIGs) are rare malignant lesions that mostly occur in brain midline regions and affect both of the pineal and suprasellar areas (7,8,12,14). Germinomas account for approximately 60% to 70% of the germ cell cerebral tumors, so they are the most frequent germ cell tumor that may affect cerebral structures (8,14). PIG represents approximately 8% of intracranial tumors in the pediatric age group patients (14). PIGs occur frequently in the first two decades of life and are usually diagnosed between 10 and 21 years of age (7,12).

The presenting symptoms vary according to lesion localization. The clinical presentation varies between obstructive hydrocephalus, diabetes insipidus, Parinaud's syndrome, hypopituitarism and visual defects. The general opinion among neurosurgeons is to obtain a biopsy using stereotactic guide

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or direct surgery to confirm the histopathological diagnosis followed by whole brain or in some cases craniospinal radiotherapy (RT)(1,3). On the other hand, radiotherapists prefer a strategy that includes "soft" preliminary radiation to assess the radiosensitivity of the tumors and to confirm the presumptive neuroradiological diagnosis before definitive RT is performed (3,10). Rarely, some patients suffer local recurrences or seeding metastasis to the central nervous system (CNS) even many years after the diagnosis. This phenomenon is poorly recognized in the literature (3). However, general agreement exists that supratentorial PIGs may definitely be cured (3).

Herein, clinical outcomes and properties of five consecutive PIGs have been evaluated.

MATERIAL and METHODS

After approval by our institute review board, the medical records of 1,849 cases of intracranial tumors, who were operated in our department of neurosurgery between 2005 and 2015, were retrospectively reviewed. The cases that were histopathologically confirmed as "germinoma" were included in this study. The clinical outcomes were evaluated retrospectively using patients' complaints, the periods between the first complaint and surgery, localization, recurrence rate and complications. All patients underwent a craniotomy/keyhole before neurosurgical tumor removal. Two patients who presented with hydrocephalus were treated surgically using a ventriculoperitoneal shunt. Standardized follow-up was carried out in all survival patients in our study. Full neurological examination and contrast-enhanced craniospinal magnetic resonance imaging (MRI) were performed one month after the treatment (surgical intervention+chemotherapy+RT). Then, every three months, the patients were examined neurologically. If there was no complaint, contrast-enhanced craniospinal MRI was performed every six months.

Illustrative Case

An 8-year-old girl was referred to our emergency department with headache of 2 weeks and nausea and vomiting in the last 2 days. Contrast-enhanced MRI demonstrated a heterogeneously-enhancing mass lesion in the suprasellar region that was well-circumscribed and measuring 43.8x33.4x44 mm with obstructive hydrocephalus (Figure 1). The patient underwent 2 operations; first, an external ventricular drain was placed for the treatment of hydrocephalus, and then the suprasellar lesion was subtotally resected using a right interhemispheric transcallosal approach (Figure 2). The histopathological examinations confirmed the diagnosis of "germinoma" with strong immunoreactivity for placental alkaline phosphatase (PLAP) and C-kit (CD 117) (Figure 3). During the follow-up period, the pituitary gland function became insufficient (sodium was 167 mEq/L). After consulting pediatric endocrinology, the patient was treated with minirin® (desmopressin acetate) 60 mg 2x1/2, deltacortil® (prednisolone) 10 mg 2x1 and euthyrox® (levothyroxine sodium) 25 mcg 1x1. The patient was then referred to the oncology department where she received 6 cycles of chemotherapy (ChT) one month after the surgical intervention, followed by 17 cycles of radiotherapy; 10 fractionated radiotherapy (FR)/18 Gy in the first phase and 7 FR/12 Gy in the second phase. Postoperative 15th and 27th month MRI showed that no residual/recurrent tumor (Figure 4) and the patient was kept on deltacortil® (prednisolone) 10 mg 2x1/2 and euthyrox® (levothyroxine sodium) 50 mcg 1x1 treatment, while minirin® (desmopressin acetate) was stopped (last two month). She was well and neurologically intact with good school performance. Craniospinal MRI showed no drop seeding metastasis after follow-up for 27 months.

RESULTS

Five cases of PIG were detected in two female (40%) and 3 male (60%) patients. The mean age was 15.2±5.6 (8-23) years. The mean follow-up period was 52.3±56.4 (9-135) months. The most common complaint was headache (60%), which was followed by nausea±vomiting (40%), while diplopia, blurred vision, emotional changes, generalized seizure, diabetes

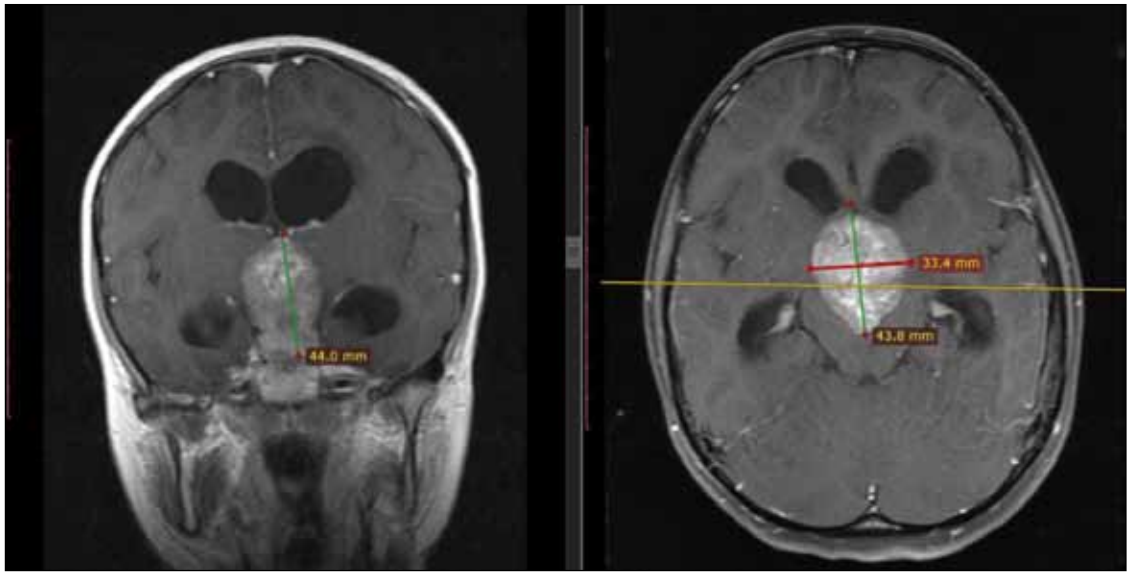

Figure 1: Preoperative coronal (left) and axial (right) contrast-enhanced MRI; T1-weighted images with contrast demonstrated heterogeneous enhancement after contrast, well-circumscribed and measuring 43.8x33.4x44 mm and there was obstructive hydrocephalus.

insipidus, unsteady gait, hemiparesis and urine retention were noticed at once (Table I). Suprasellar region was involved in four cases while the fifth patient's tumor was in the pineal region. The duration between the initial symptom and time of surgical intervention ranged between 15 days and 2 months. Twelve months after the first operation, one patient presented with unsteady gait, tingling and weakness in the lower extremities bilaterally. His contrast enhanced craniospinal MRI demonstrated intradural-intramedullary lesion which had an extradural compartment and syringomyelia which extended to C3 above the lesion. The lesion was confirmed to be germinoma. Another child died after one week of operation related to surgical complications in which brainstem damaged intraoperatively. Three cases were treated by near total and

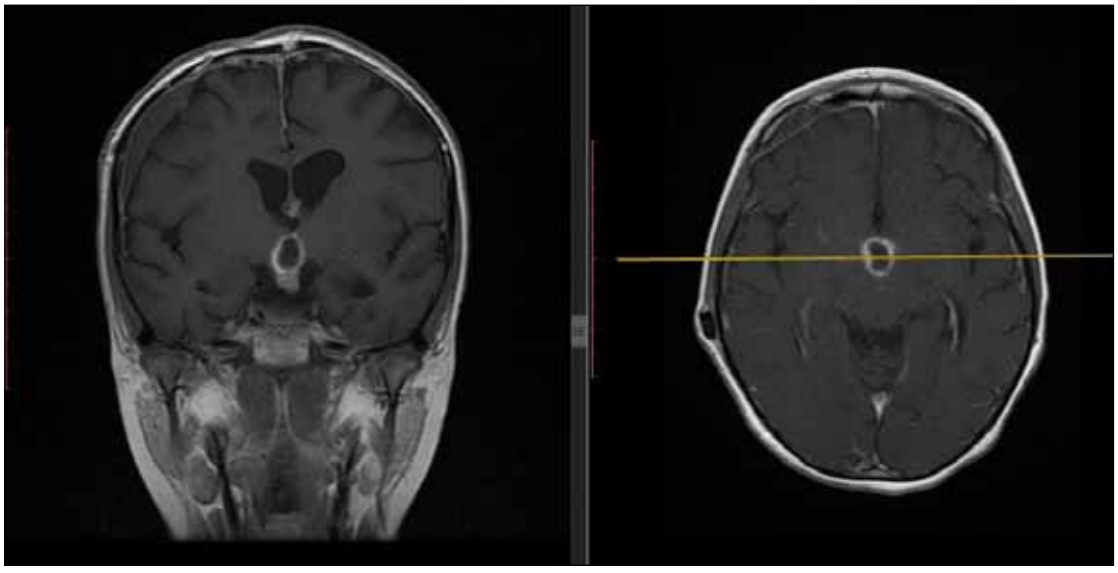

Figure 2: Postoperative first month coronal (left) and axial (right) contrast-enhanced MRI; T1-weighted images with contrast showed postoperative changes.

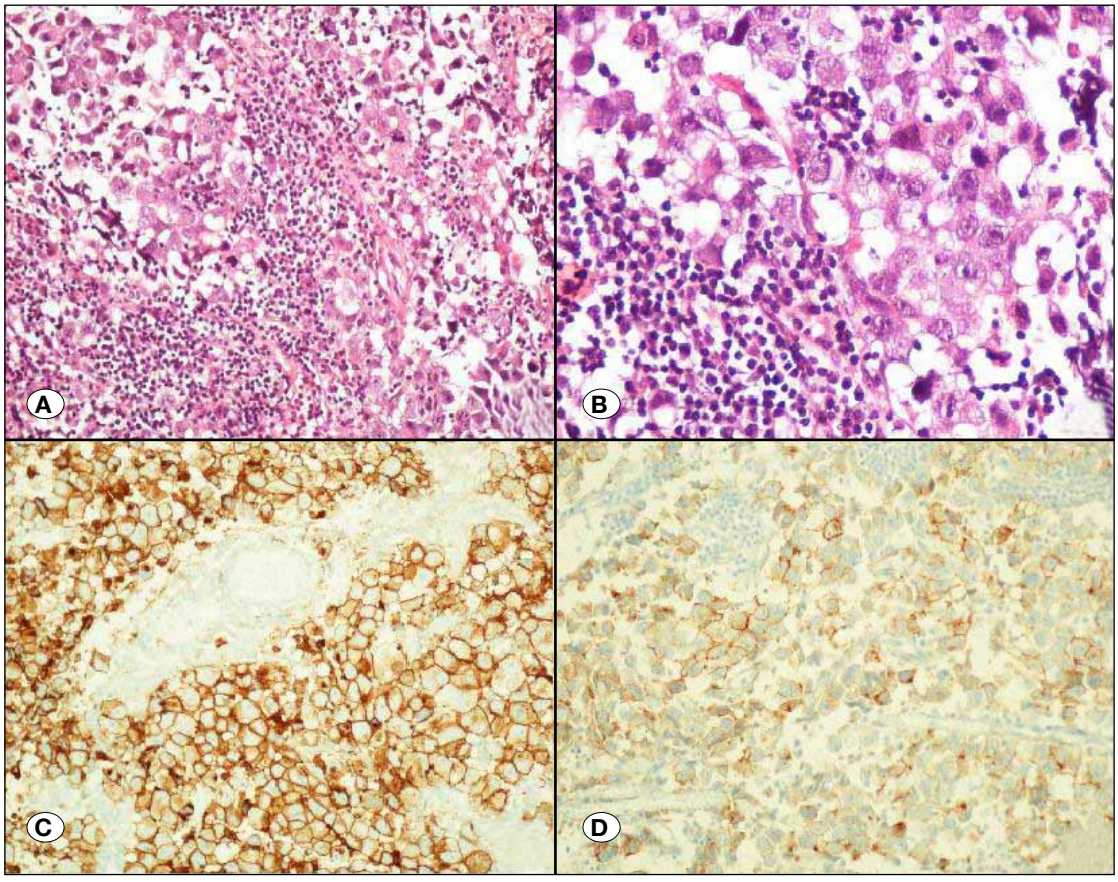

Figure 3: The histopathological examinations confirmed that the mass was a germinoma with strong immunoreactivity for PLAP (placental alkaline phosphatase) and C-kit (CD 117). **(A)** and **(B)** Histopathological findings revealed large tumor cells (germ cells) and lymphocytic cells **A)** Hematoxylin-eosin stain, x200; **B)** Hematoxylin-eosin stain, x400; **C)** PLAP (specific marker for germinoma) was strongly positive (immunhistochemical stain, x200); **D)** C-kit (CD 117) was positive (immunhistochemical stain, x200).

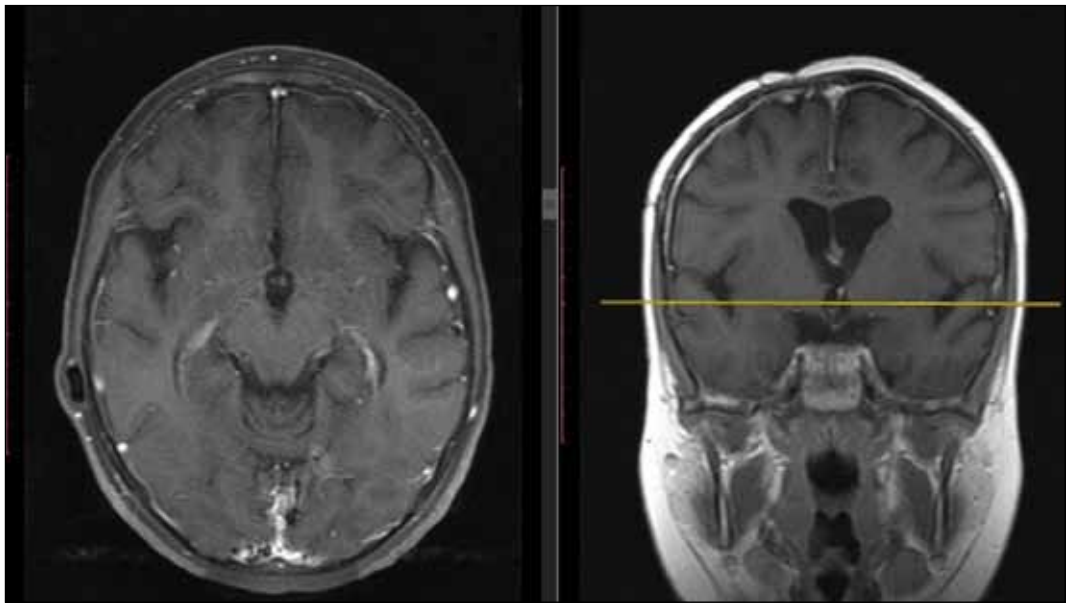

Figure 4: Postoperative 27th month axial (left) and coronal (right) MRI; T1-weighted images that demonstrated postoperative changes without recurrence or residual tumor.

subtotal resections. Then, the cases were referred to oncology department and received RT and ChT. Five-year survival (with exception of the case who died due an early surgical complication) was 100%. Gross total resection (GTR) was achieved in one patient who died one week after the surgical intervention, i.e. surgical mortality rate was 20%. Other patients in this series treated using (near-total resection(NTR)/ subtotal resection(STR)+ChT+RT) approaches which gave good results. Tumor-related morbidity rate was 60%. Two (40%) patients presented with hydrocephalus and treated with ventriculoperitoneal (VP) shunt. One of them had meningitis and generalized seizure before the VP shunt placement (Table I). Local recurrence was not detected.

■ DISCUSSION

The World Health Organization (WHO) divided germ cell tumors (GCT) of the CNS, into benign (mature teratomas) and malignant (germinoma and non-germinoma) tumors (7). Intracranial germ cell tumors represent 0.3% to 3.4% of all primary intracranial lesions (6). Germinomas are the most common GCTs in the brain, as they constitute about 65% of all intracranial GCT (6). PIGs typically affect brain midline regions such as suprasellar, pineal and cerebellar vermis (6,9). Spinal cord metastases have been reported in 10% to 20% of patients (2). In our series of the intracranial tumors who underwent surgery between 2005 and 2015 years, PIGs account for about 0.27% (5/1849) of the cases. One of our patients experienced drop (seeding) spinal cord metastasis, i.e., 20% of our patients had spinal cord metastases.

Most of these cases were children or young adults. Expect one of our patients who was a 23-year-old male, all of our patients were less than 18 years old. The mean age of onset in our series was 15.2±5.6 (8-23) years and this age is close to reported mean age in the literature which is about 17 years (5,9).

PIGs generally occur in the suprasellar and pineal regions, and both regions may be affected in 8% of the patients (6). Our series showed four cases were located in the suprasellar and one case was in the pineal region. Unlike many of GCT members, our cases of PIGs do not consistently alter serum levels of β-human chorionic gonadotropin (β-hCG) and alpha-fetoprotein (AFP). In all our cases, histopathological examinations showed strong immunoreactivity for PLAP and C-kit (CD 117), with negative serum levels of β-hCG and AFP. In our series, there was a higher prevalence in males, with three of our cases male and two patients female, similar to the literature that showed a male to female ratio of 1.88:1 (5,6,9).

Clinical presentation of PIG patients depends on the location and the size of the lesion. In cases that affect suprasellar region, patients usually present with hypothalamic or pituitary dysfunction, isolated diabetes insipidus, or in association with other hormone deficiencies (12). In some cases, papilledema with restriction of upward gaze and convergent nystagmus on attempted upgaze (Parinaud's syndrome) may be the presenting symptom. Ophthalmic abnormalities such as bilateral hemianopsia may also be present. The most common complaints in our patients were headache in 3 of our patients (60%), followed by nausea±vomiting in two cases (40%) (Table I). The duration between the initial symptom and time of surgical intervention ranged between 15 days and 2 months. Two patients of our series presented with headache, nausea and vomiting, when computed tomography (CT) and MRI were performed. Cranial CT and MRI demonstrated obstructive hydrocephalus, and firstly surgical intervention was performed to treat hydrocephalus using a VP shunt and external ventricular drainage and then surgical intervention for the mass lesion was performed.

Although combined therapy of RT and ChT is the treatment of choice for PIGs, RT is the standard treatment for these lesions and provides cure in more than 90% of patients (4).

Table I: Baseline Clinical Characteristics, Treatment and Outcomes of Treatment

No	Clinical Presentation	Age (Years)/ Sex	Location	Admission Period	Treatment	Postoperative Course	Survival after Surgery
1	Nausea, vomiting, unsteady gait, urinary retention, hemiparesis	17/M	Pineal	10 dys	NTR+ChT+RT	PO 12.mn presented w/unsteady gait, MRI: Intradural-intramedullary lesion (drop seeding metastasis) which has a extradural compartment and syringomyelia which extended to C3 above the lesion. Pt underwent the operation and treated successfully.	Alive; 135 mns
2	Headache, emotional changes, generalized seizure	12/M	Suprasellar	1 wk (ex)	GTR	Died one week after operation (related to surgical intervention).	Died; 7 dys
3	Headache, diplopia, blurred vision	23/M	Suprasellar	7 dys	STR using Stx-Guide+ ChT+RT	First VP shunt was placed to treat hydrocephalus, then treated w/ diplopia.	Alive; 38 mns
4	Headache, nausea, vomiting,	8/F	Suprasellar	28 dys	STR+ChT+RT	First EVD was placed then STR, PO 3.dy DI, PO 10.dy generalized seizure after involved with meningitis caused by acinetobacteria; medical treatment then VP shunt.	Alive; 27 mns
5	Diabetes Insipidus	16/F	Suprasellar	13 dys	Endoscopic Endonasal GTR+ ChT+RT	Symptoms are under control (minirin® and deltacortil®).	Alive; 9 mns

GTR: *Gross-total resection,* ***NTR:*** *Near-total resection,* ***STR:*** *Subtotal resection,* ***RT:*** *Radiotherapy,* ***ChT:*** *Chemotherapy,* ***Stx-Bx:*** *Stereotactic biopsy,* ***dys:*** *days,* ***wks:*** *weeks,* ***mns:*** *months,* ***yrs:*** *years,* ***F:*** *Female,* ***M:*** *Male,* ***Met:*** *Metastasis,* ***PO:*** *Postoperative,* ***VP shunt:*** *ventriculoperitoneal shunt,* ***EVD:*** *External ventricular drainage,* ***Ex:*** *Exitus,* ***MRI:*** *Magnetic resonance imaging.*

Some oncology centers suggest a radiation dose of 50 Gy, but these lesions can be cured with doses less than 50 Gy (4,13). Actually, four of our patients had cure with combined ChT and RT using doses less than 50 Gy after the surgical intervention.

Seeding metastasis is uncommon phenomenon which happens generally with high grade malignant intracranial lesions and sometimes with those arising intraspinally. Neuraxis spreading of malignant high-grade tumors especially have been noticed in children more often than adults. When the origin (primary focus) of seeding metastasis (neuraxis dissemination) is an intracranial tumor and the seeding metastasis happens in the spinal cord, the condition is called "drop metastasis". Spinal cord metastases were reported in 10% to 20% of PIG patients (2). Although all of our patients (who were still alive after surgery) received RT and ChT, one of them who was a 17-year-old male experienced drop spinal cord metastases one year after the surgical intervention. The patient presented with unsteady gait, tingling and weakness in the lower extremities bilaterally, 12 month after the first operation. His craniospinal MRI demonstrated intradural-intramedullary lesion which had an extradural compartment and syringomyelia which extended to C3 above the lesion. The patient subsequently underwent total fifth and sixth cervical laminectomy, and gross-total resection of the mass was achieved. Histopathologically, the mass was confirmed to be a germinoma.

Packer et al. suggested that biopsy-proven germinomas can have non-germinomatous elements among the unbiopsied sites (11). In a similar way, non-secreting tumors can also have non-germinomatous components such as immature teratoma with less favorable prognosis (11). On the other hand, PIGs are radiosensitive tumors. GTR (i.e., resection of the tumor till reaching paranchymal structure) for germinomas is difficult, because of the location of these lesions which are mostly around brain midline regions such as the pineal and suprasellar areas. GTR of germinomas may lead to damage brain midline structures such as brainstem, or occult the vascular structures that supply important neural structures there. All of this may lead to death of the patient. Herein, the neurosurgical team recommend subtotal 'STR' or near total resection 'NTR' (i.e., decompressing the tumors' neighbouring midline brain structures and excising more than 75% 'STR' or 95% 'NTR' of tumor mass with leaving the parts of tumor attached to the brainstem or midline neurovascular structures) to confirm the diagnosis (as it is important to know what kind of tumor is arising there) and reducing the possibility of non-germinomatous component residue and then referring the patients to receive ChT and RT which is curative treatment and leads to good results rather than GTR. In our series, GTR was performed in one child which thought to be non-germinomatous GCT even serum level of both of AFP (<10μg/L) and β-hCG (<30 mIU/ml) were in normal ranges. Postoperatively, the patient was localized pain [i.e. his Glasgow Coma Scale was 7 (E1V1M5)] and the radiological studies showed an infarction in the brainstem. The patient died one week after surgical intervention, i.e. surgical mortality rate was 20%. The authors do not recommend biopsy alone and think that decompressing the tumors' neighbouring midline brain structures by subtotal or near-total resection rather than GTR may be help adjuvant therapies (ChT and RT) to be curative. In the same way, the tumors located in midline brain regions will be combined with a lot of complications such as obstructive hydrocephalus, diabetes insipidus, Parinaud syndrome, hypopituitarism and visual defects. Tumor-related morbidity rate of PIG was 60%; two patients presented with hydrocephalus and treated with VP shunt. One of them had meningitis and experienced generalized seizure before VP shunt placement (Table I).

RT does not prevent the late development of recurrence and spinal cord metastasis. Franzini et al.(3) reported fatal recurrence in 15% of their twenty patients. One of our series experienced drop cervical metastasis after one year of operation and adjuvant ChT and RT, while no recurrence was detected in our series.

CONCLUSION

Primary intracranial germinoma is a mostly malignant tumor that generally affects the pediatric age group. It is a radiosensitive tumor, therefore, subtotal or near-total resection using stereotactic guide or direct surgery to confirm the histopathological diagnosis is followed by ChT and RT. This approach may decrease complications of gross-total resection and may control local recurrence and drop seeding metastasis and keep both at minimal rates as well. Authors pointed out that NTR or STR is important to reduce the possibility of the local recurrence and neuraxis dissemination. GTR is not a significant prognostic factor in outcome for patients with PIG as well as the importance of an early diagnosis in order to improve the prognosis of the tumor and the necessity of a careful follow-up of these cases.

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