

Primary Intracranial Germ Cell Tumors: A Single-Centre Experience.Shagufta T. Mufti (MBBS, MD)¹, Saleh S. Baesa (MD, FRCSC)², Jaudah A. Al-Maghrabi^{1,3} (MD, FRCPC)Departments of Pathology¹ and Neurosurgery², Faculty of Medicine, King Abdulaziz University Department of Pathology³, King Faisal Specialist Hospital and Research Centre, Jeddah, Saudi Arabia
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Abstract: Background: Primary intracranial germ cell tumors are rare (PICGCTs) tumors that share histological features with gonadal GCTs and usually present diagnostic difficulties. The aim of this study is to present pathological and radiological findings of PICGCTs diagnosed at a tertiary medical centre in the western region of Saudi Arabia along with review of recent literature. **Methods:** We retrospectively analyzed the pathological and clinical data of patients diagnosed with PICGCTs in King Faisal specialist hospital and research centre (January 2001 to December 2012). **Results:** Eight cases were diagnosed as PICGCTs. Seven cases were males in their pediatric age group with a mean age of 11.11 years. The overall mean age was 12.39 years. Three cases were located in the pineal region 37.5 % (3), two were located in the mid brain 25% (2) and one each (12.5%) was located in posterior fossa, hypothalamus and suprasellar region. On histological examination 50% (4) were purely germinomas, followed by 25% (2) mixed germ cell tumors (MGCTs) and 25% (2) immature teratomas (IT). **Conclusion:** PICGCTs are rare tumors affecting mainly adolescent males more than females with their added site predilection for the pineal region. Pure germinoma is the most common pathological type.

[Shagufta T. Mufti, Saleh S. Baesa and Jaudah A. Al-Maghrabi. **Primary Intracranial Germ Cell Tumors: A Single-Centre Experience.** *Life Sci.* J.2013;10(1):1709-1715]. (ISSN: 1545-1003). <http://www.lifesciencesite.org>. 249

Key Words: Intracranial, pineal, germinomas, immunohistochemical, radiological

1. Introduction

Germ cell tumors (GCTs) in uncommon locations usually present diagnostic difficulties^[1]. They are a heterogeneous group that are widely considered to be morphologic and immunophenotypic homologues of germinal neoplasms arising in the gonads and other extragonadal sites^[1]. The World Health Organization (WHO) classification of GCTs of the central nervous system (CNS) is similar to that of other sites: germinoma (denoted as seminoma in the testis and dysgerminoma in the ovary), teratoma (mature, immature, and with secondary malignancy), yolk sac tumor, embryonal carcinoma, choriocarcinoma, and mixed tumors^[1]. Primary intracranial germ cell tumors (PICGCTs) are however a curious form of neoplasm. The fact that they arise in specific locations in the brain: the suprasellar and pineal region, their histogenesis and cell of origin are all debatable aspects^[2]. This retrospective study was undertaken to present the pathological and radiological findings in eight cases of histologically confirmed primary intracranial germ-cell tumors along with review of recent literature in order to enhance our understanding regarding these rare and intriguing tumors.

2. Methods**Study setting and population:**

A retrospective study of all histopathologically diagnosed primary intracranial germinomas in the period between January 2001 and December 2012 was performed through a computerized data base search of the Anatomic Pathology archives at King Faisal Hospital and Research Centre (KFHRC), Jeddah.

Data collection:

The data was filtered using appropriate morphology SNOMED (Systematized Nomenclature of Medicine) codes indicating the following parameters: Date of receiving biopsy, demographics, clinical diagnosis, morphology and radiography. Eight cases of PICGCTs were retrieved and classified using WHO classification system^[1]. Clinical and radiological correlation was evaluated. Sufficient blocks for each specimen were submitted in order to ensure sampling adequacy. All cases were processed as per standard histopathological techniques, which include paraffin embedding, and Hematoxylin and Eosin staining. Microscopic examination was done by two pathologists separately to determine the type of different components of the tumor. Immunohistochemical staining using an automated stainer with the avidin-biotin-peroxidase complex method was performed using the antibodies Pan cytokeratins (CK-PAN: dilution 1:50; Dako, Carpinteria, CA, USA), Placental alkaline phosphatase (PLAP: dilution 1: 50; Dako, Carpinteria, CA, USA), CD117 (c-kit: dilution 1: 50; Dako,

Carpintena, CA, USA). Antibodies such as Chromogranin (CHR), Human chorionic gonadotropin (HCG), Leucocyte common antigen (LCA), OCT 4 (POU family transcription factor) and Synaptophysin (SYN) were all available as ready to use kits (Ventana, Rocklin, CA, USA). Antibodies were used to highlight the various histological components as and when the case scenario necessitated. Results were scored as follows: -, not seen; +/-, rare/focal positivity; +, diffuse positivity. Positive and negative controls were performed for the stain. Clinical data were obtained from the patients' hospital records and follow up was obtained on personal basis from the concerned neurosurgical, radiological and medical teams.

We analyzed the medline literature search of the reported studies including epidemiological studies and diagnostic articles about PICGCTs in the English literature from 2000-2012 through the national library of medicine, Pubmed, and OVID search engines. We used key words "intracranial germ cell tumors", "pineal germinoma," "pineal gland tumor," and "CNS germinoma," for Medline search.

Statistical analysis:

Data were analyzed using the program Statistical Package for the Social Sciences, version 15.0 (SPSS Inc., Chicago, IL, USA). The procedures followed in the present study were in accordance with the ethical standards of the hospital ethical committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2000.

3. Results

Seven out of eight cases in the present study were males in their pediatric age group with a mean age of 11.11 years. The overall mean age was 12.39 years including one case of 3 months old girl and 26 years old young man. Three cases were located in the pineal region 37.5 % (3), two were located in the mid brain 25% (2) and one each (12.5%) was located in posterior fossa, hypothalamus and suprasellar region.

Radiological findings of the MRI and CT brain were available in only six of the eight cases and are presented in Table 1 and Figure 1 a-c and 2 a-d. Radiological examinations such as X-ray and CT scan (computerized tomography) performed for the chest; abdomen and pelvis in all cases were clear with no focal lesions identified. The testis were free radiologically and clinically in all the cases excluding the possibility of metastasis from an occult primary in the gonads. Radiological follow up at 6–9 months showed no evidence of residual tumor in 2 (25 %) cases at the pineal region. Two cases (25 %) showed residual tumor at follow up of 1 year. One of them was located in the midbrain region of a 26 year old

male and the other was located in the pineal region of a 9-year old boy.

On histological examination 50% (4) were purely germinomas in male patients with mean age of 16.25 years followed by 25% (2) mixed germ cell tumors (MGCTs) in male patients with mean age of 16.5 years and 25% (2) immature teratomas (IT) among male infants with a mean age of 7 months. Among the MGCTs the frequent combination in the two cases was that of germinoma and mature teratoma. Pathological and immunohistochemical findings are presented in Table 2 and Figure 3 a-c.

4. Discussion

PICGCTs constitutes nearly 2 to 3% of pediatric brain tumors^[3,4], with 85% of them occurring before the second decade of life^[5]. The incidence of PICGCTs shows wide geographical and ethnic variation between Asian and Western regions^[6]. The comparative incidences of PICGCTs are 27.4% in Korea^[7,8], 14.3% in Japan^[9], 14.0% in Taiwan^[10], 5.4% in Mexico^[11] and 2.3% in USA^[11] in various reported series. However a recent population based study revealed that the incidence of PICGCTs is similar between Japan and United States and has the same gender-based patterns by location^[6]. The peak incidence of PICGCT is during the second decade of life, with a median age at diagnosis of 10 to 12 years^[12]. A case-report in a 59-year-old male patient with a pineal and sellar lesion has been added to literature recently^[13]. There is a male preponderance ranging between 2:1 to 3:1, especially with tumors in the pineal region^[12]. Pineal location is strongly associated with male sex; with pineal germinomas representing over half of all CNS GCTs in males^[5]. The reported incidence of PICGCTs in children is significantly higher in Asian countries compared to Western countries. In Western countries, PICGCTs account for 0.4%–3.4% of all pediatric CNS tumors^[12], while recent epidemiological study from Japan reported that PICGCTs were the second-most common tumors (14.3%, annual incidence 5.0 per million) affecting mainly 10-14 years old boys^[9]. We found view of literature revealed no reasonable explanation in the reviewed literature for this significant geographic and ethnic variation between the Asian and Western study groups. To the best of our knowledge only one case of midbrain germinoma has been reported so far from Saudi Arabia^[14].

Among the 363 malignant and nonmalignant GCT identified in the CBTRUS by Villano et al^[15], 35.5% were located in the pineal region. Of the remaining nonpineal GCT, the most common site was the brain, NOS (not otherwise specified) 31.6%, followed by the ventricles 17.1%, the pituitary 14.1%, and the cerebrum 9.8%.

Table 1: Radiological features of PICGCTs at KFHC, Jeddah, Saudi Arabia

Age/Sex	Radiological findings		
	Mri Brain	CT BRAIN	Post Resection/Treatment Mri Brain
Case 1 2001 15 year old boy	NA	NA	NA
Case 2 2002 3 months old girl	NA	NA	NA
Case 3 2004 17 year old boy	Large mixed signal intensity mass at the pineal region measuring 4.8 x 3.3 x 3.3 mm with solid and cystic components with heterogeneous signal intensity on T2. Post Gadolinium contrast showed heterogeneous enhancement in the solid component with mild hydrocephalous and calcifications.	Complex heterogenous lesion at the pineal gland	No evidence of enhancing residual lesions or mass effect in the pineal region on 6 months radiological follow up available
Case 4 2005 16 year old boy	Mixed signal intensity mass at the pineal region measuring 2.8x3x2.3 mm with solid and cystic components . Post Gadolinium showed minimal enhancement in the solid component	NA	No evidence of enhancing residual lesions or mass effect in the pineal region on 9 months radiological follow up available
Case 5 2006 15 year old boy	Midline homogenously enhancing hypothalamic tumor measuring 1.2x 0.7 mm No cystic component seen	Hyperdense hypothalamic lesion	No evidence of enhancing residual lesions or mass
Case 6 2007 26 year old male	Heterogeneous signal intensity tumor measuring 3.1x2.1x1mm at the corpus callosum extending to the mid brain measuring .Lesion exhibits solid and cystic components . Post Gadolinium shows enhancement of solid component with obstructive hydrocephalus	Mass at the corpus callosum cms with dilation of measuring 3.1x2.1x1 mm involving the mid brain	Residual tumor measuring 2.5x2.1 mm with no significant interval changes on 1 years radiological follow up available
Case 7 2010 11 month old boy	Large suprasellar solid and cystic mass measuring 6.8x4.4x3.2 mm with heterogeneous signal intensity on T2.Post Gadolinium shows enhancement of the solid component with severe obstructive hydrocephalus	Large suprasellar solid and cystic mass measuring 6.8x4.4x3.2 mm with compression of brain stem and obstructive hydrocephalus	Complete resection of suprasellar tumor with tiny residual interpeduncular cistern with persistent hydrocephalus on 1 and 1/2 years radiological follow up
Case 8 2011 9 year old boy	Complex solid and cystic tumor at the pineal gland measuring 2.3x1.4 mm. Post Gadolinium shows homogenous enhancement of the solid component with obstructive hydrocephalus	Well defined hyperdense mass measuring 2.4x1.5 mm with punctuate calcifications	Marked reduction in tumor size at 6 months with no significant interval changes in residual tumor on 1 year radiological follow up

MRI: magnetic resonance imaging NA: not available

CT: Computerized tomography

Table 2: Pathological and immunohistochemical features of PICGCTs at KFHC, Jeddah, Saudi Arabia

Age/Sex	Primary location	Histological type	Immunohistochemical profile
Case 1 2001 15 year old boy	Mid brain	Germinoma	PLAP +ve HCG -ve
Case 2 2002 3 months old girl	Posterior fossa tumor	IT	*
Case 3 2004 17 year old boy	Pineal region	MGCT (Germinoma 25%with MT)	*
Case 4 2005 16 year old boy	Pineal region	MGCT (Teratomatous component 65% , YST 30%,Seminoma less than 5%)	*
Case 5 2006 15 year old boy	Hypothalamus	Germinoma	PLAP +ve CK-PAN & LCA -ve
Case 6 2007 26 year old male	Mid brain and Corpus callosum	Germinoma	PLAP +ve LCA,CK-PAN & Vim -ve
Case 7 2010 11 month old boy	Suprasellar	Teratoma with immature elements 10% and neuroendocrine elements 50%.	CHR ,SYN +ve in carcinoid areas
Case 8 2011 9 year old boy	Pineal region	Germinoma	CDII7+ve, OCT 4 +ve PLAP and CD 15 focally +ve

Mixed germ cell tumor :MGCT	Human chorionic gonadotropin hormone: HCG
Yolk sac tumor:YST	Pan cytokeratin:CK-PAN
Immature teratoma:IT	Chromogranin:CHR
Mature Teratoma:MT	Leucocyte common antigen: LCA
Positive:+ve, Negative : -ve, &:and *:Immunohistochemical markers were not required for morphological assessment	:OCT 4 Synaptophysin:SYN, Vim:vimentin Placental alkaline phosphatase:PLAP

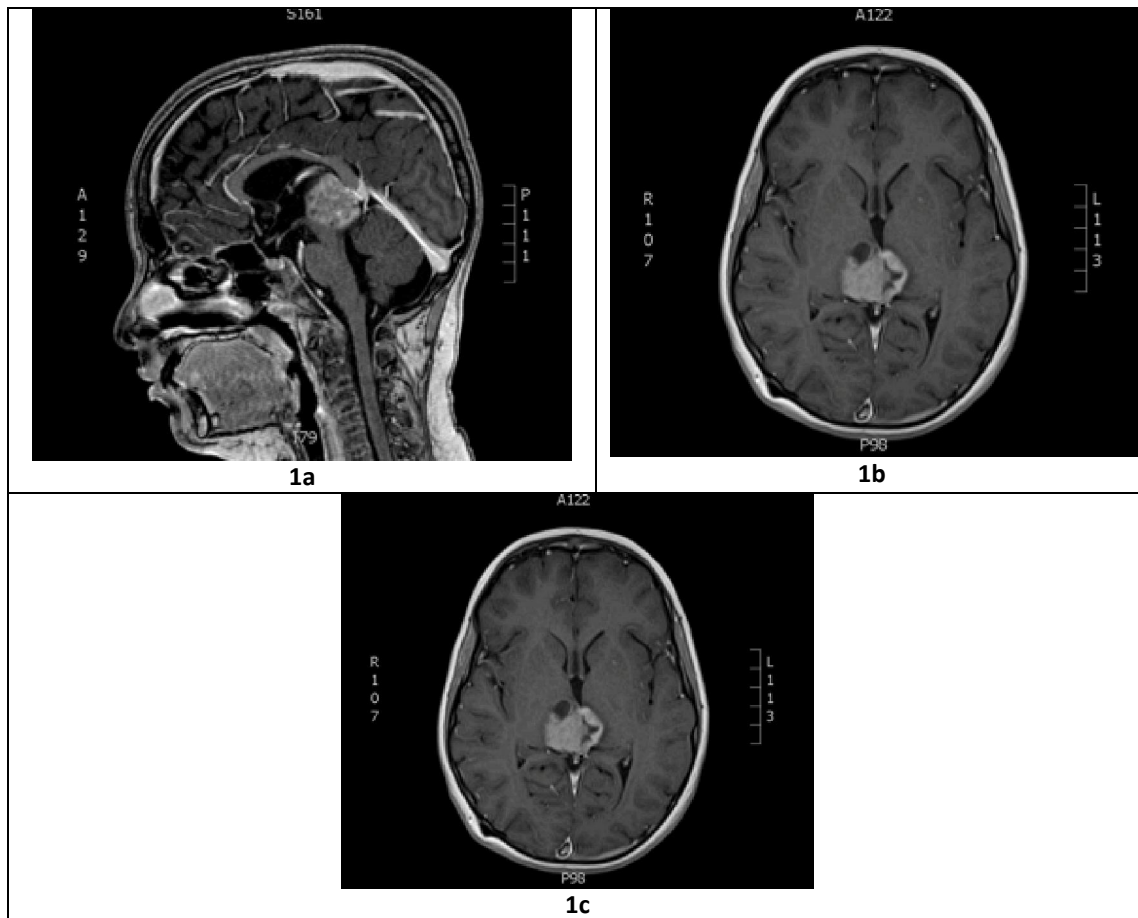
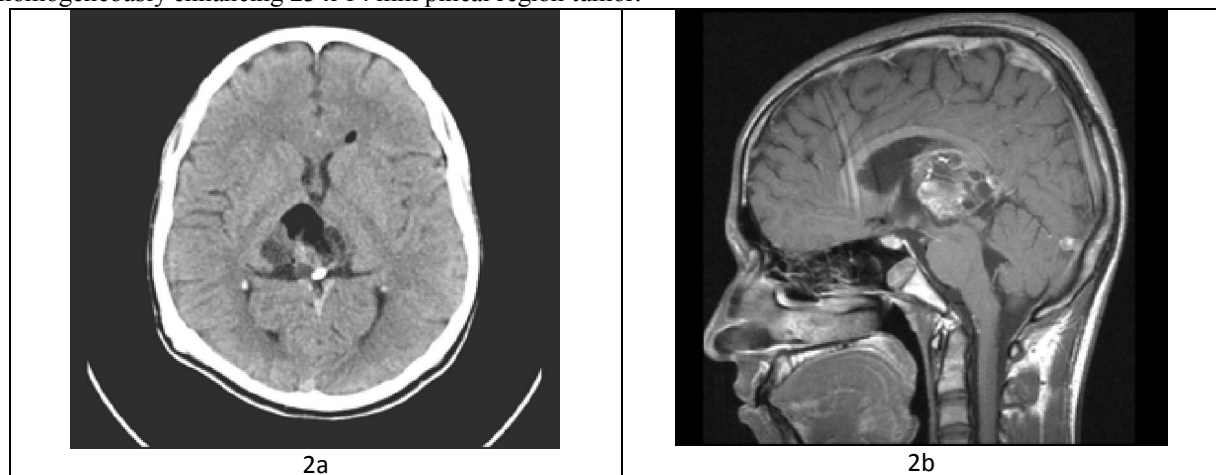


Figure 1: A 9-yr-old male (case 8) presented with headache due to obstructive hydrocephalus, treated with VPS. Gadolinium-DTPA enhanced cranial MRI scans (a) sagittal, (b) axial, and (c) coronal demonstrating cystic homogeneously enhancing 23 x 14 mm pineal region tumor.



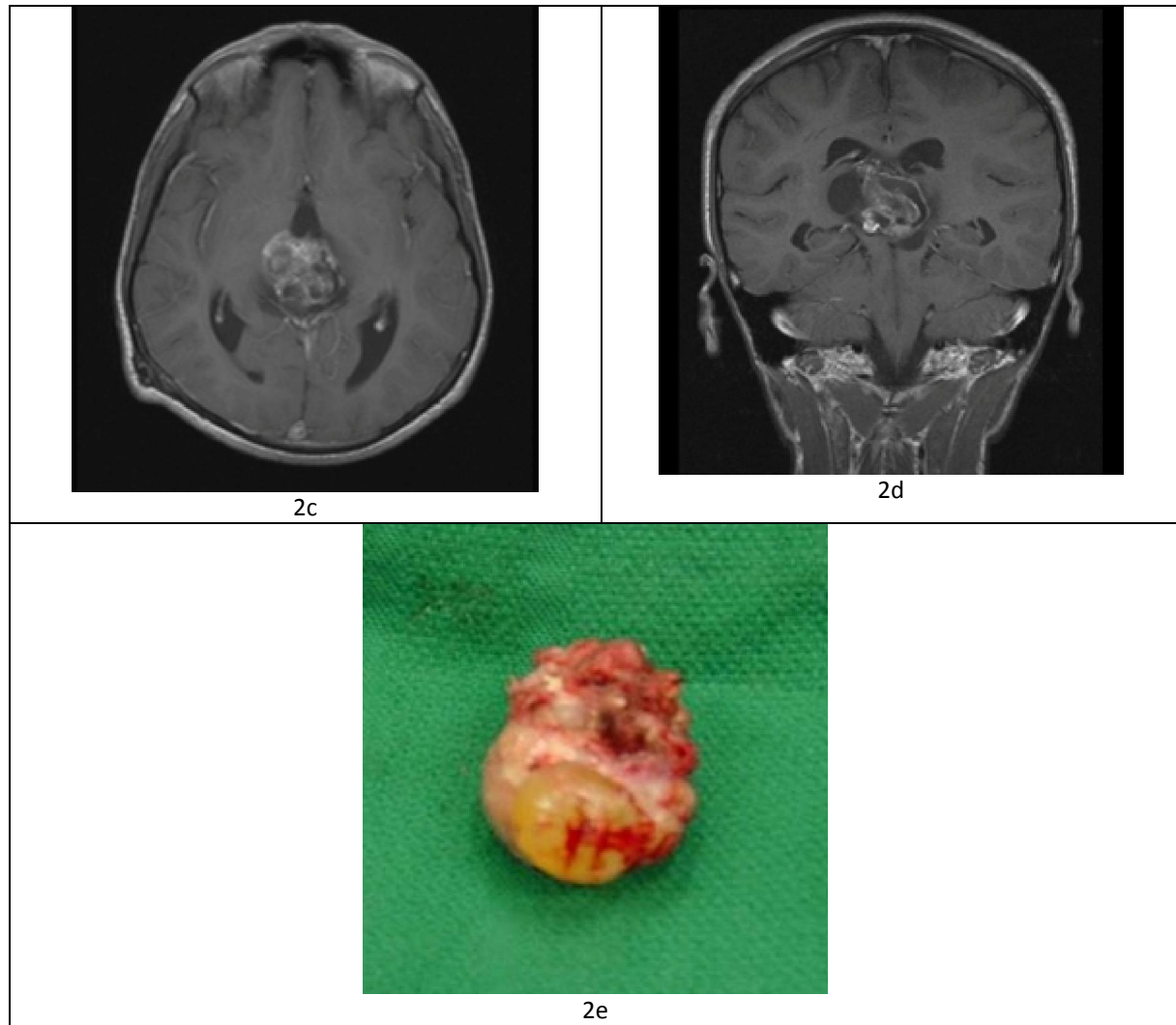
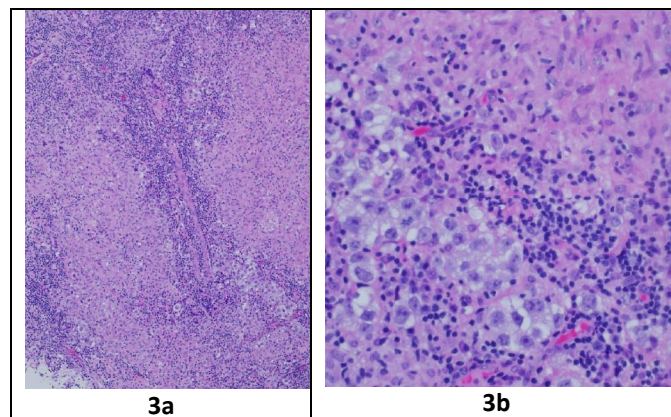


Figure 2: A 17-yr-old male (case 3) presented with headache and vomiting and blurred vision. Non-enhanced cranial CT scan (a) demonstrating a 48 x 33 mm heterogeneous pineal tumor; it has densities consistent with fat and calcifications. Gadolinium-DTPA enhanced cranial MRI scans (b) sagittal, (c) axial, and (d) coronal demonstrating heterogeneously enhancing pineal region tumor. The ventricles are well decompressed after insertion of right-sided ventriculoperitoneal shunt (VPS). Photographic image (e) demonstrate gross feature of the resected pineal tumor.



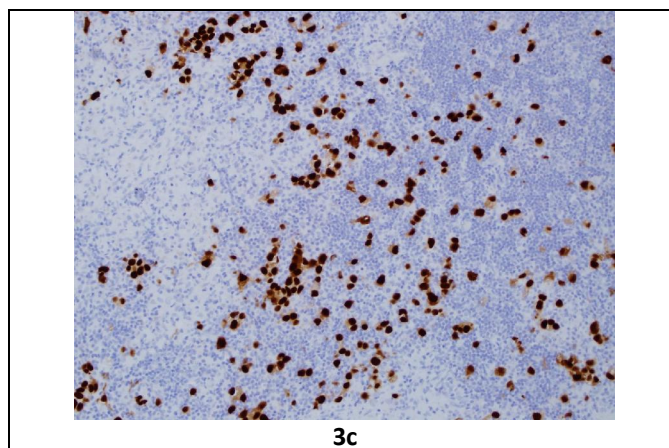


Figure 3: Microscopic features of the pineal tumor from a 9-yr-old male (case 8) showing (a) Sheets of atypical large cells with round, oval and reniform nuclei, some with prominent nucleoli and a variable amount of pale cytoplasm. These cells are intimately mixed with the small lymphoid cells. (b) Immunohistochemistry shows strong staining in the atypical large cells for OCT 4.

Lee D and Suh YL ^[7] reported suprasellar region accounting for 64.5% of the nonpineal GCT. Unusual loci reported for PICGCTs in the CNS, include the basal ganglia, thalamus, fourth ventricle, corpus callosum ^[3,16], intrasellar ^[17] and spinal cord ^[18]. PICGCTs of the midbrain are extremely rare ^[19]. Nonetheless, PICGCTs should be considered in the differential diagnosis if a mass is encountered in the brainstem, especially if it exhibits mixed signal profiles ^[20].

There are two prevailing theories on the development of these tumors ^[15]. The “germ cell theory” which proposes that primordial germ cells (PGCs) are misplaced in migration and are the same both intracranially and extracranially ^[15]. The other theory proposes a widespread distribution of germ cells during normal embryogenesis in the brain, and that these cells provide important regulatory functions at these sites and are biologically distinct from PGC ^[15,21]. A study examining the biology and origin of PICGCTs analyzed expression of a wide panel of stem cell-related proteins (C-KIT, OCT-3/4, AP-2 γ [a homeobox gene]) and developmentally regulated germ cell-specific proteins ^[21]. The expression of genes associated with embryonic stem cell pluripotency in PICGCTs strongly suggests that these tumors are derived from cells that retain an embryonic stem cell-like phenotype, which is characteristic of PGCs ^[21].

Histologically PICGCTs are divided into two histologic patterns: germinomas (GGCT) and nongerminomas GCT (NGGCT) ^[15,22]. GGCT are histologically identical to the gonadal counterparts of seminoma (testes) and dysgerminoma (ovary) and are highly sensitive to radiotherapy and chemotherapy with high cure rates ^[22]. NGGCT, however, have a

poorer prognosis ^[15, 22]. GGCT account for 50%–70% of PICGCTs ^[12]. NGGCT are a heterogeneous group of tumors accounting for one third of PICGCTs that include pure or mixed (more common) populations of germ cell elements including embryonal carcinoma, endodermal sinus tumor, choriocarcinoma, malignant teratoma, and/or mature or immature teratoma ^[15,22]. OCT4 (also known as OCT3 or POU5F1) is emerging as a highly specific and sensitive immunohistochemical marker for primary intracranial germinomas and studies indicate that the intensity of OCT4 immunostaining is significantly better than that of PLAP ^[23].

At the molecular level frequent imbalances of chromosomes have been described in PICGCTs, including chromosomes 1, 8, 12, 13, 18 and X. Recently, p14 and c-kit gene alterations have been reported, particularly in some GGCT; however, their importance remains unclear ^[24]. Patients with Klinefelter syndrome or Down syndrome appear to be predisposed to the development of gonadal as well as intracranial germinomas ^[24].

The MRI features are very useful in the diagnosis of PICGCT. The solid components of GCTs may show homogeneous and heterogeneous enhancement, while all NGGCTs show heterogeneous enhancement, including histological subtypes ^[4]. However the neuroimaging characteristics of GCTs and NGGCTs show considerable overlap limiting the diagnostic certainty, and making tissue confirmation essential for the diagnosis ^[16]. Over 90% of localized intracranial germinomas can be effectively treated with radiation therapy and exhibit a relatively good prognosis ^[25]. The outcome for patients with NGGCTs is less

favorable ^[22]. Radiation therapy alone will result in disease control in 40%-60% of patients ^[26].

This study has certain limitation and the results should be interpreted keeping them in mind. Since PICGCTs are rare tumors the small number of cases limited our study and as such our results do not reflect the pattern of PICGCTs in the population at large.

In conclusion our study validates past observations that PICGCTs arise mainly in pineal region and show male preponderance with a mean age of 12.4 years in the present study. The most frequent histological pattern was that of germinomas, which were present among male adolescents, while non-germinomatous GCTs were present among male infants. The epidemiological variation and male predilection are suggestive of a curious but poorly understood influence of sex, either genetic or hormonal, on the occurrence of PICGCTs, which is a reasonable consideration to be kept in mind while studying these tumors.

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1/12/2013