

Pearls & Oysters: Bifocal germinoma of the brain

Review of systems is key to the diagnosis

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PEARLS

- Intracranial germinoma is the most common malignant intracranial germ cell tumor. It usually occurs in children and young adults and with the current therapies, many patients experience long-term survival.
- Suprasellar region germinoma can present with isolated hypothalamic–pituitary axis dysfunction such as diabetes insipidus, delayed growth, menstrual irregularities, or precocious puberty, while pineal region germinoma can present with features of raised intracranial pressure and Parinaud syndrome.
- Pineal and suprasellar region germinomas can coexist in the same patient. Such a combination is called a bifocal germinoma.

OYSTER

- Intracranial germinoma in a child or young adult may be easily missed if careful evaluation of review of systems with reference to endocrine functions is not undertaken.

CASE REPORT A 17-year-old girl presented to the Pediatric Neurology clinic with new onset headache of 8 weeks duration. She experienced a daily headache described as a pressure-like sensation over both the temporal areas, 4/10 in intensity. This baseline headache was interrupted by a few episodes of pounding bitemporal and occipital headache, 10/10 in severity, worse with activity. The severe headaches were associated with dizziness, photophobia, phonophobia, vomiting, and “zig-zag lights” in front of her eyes and often would occur on awakening. She occasionally described “whooshing sounds” associated with the baseline headache. On review of systems it was noted that she had poor energy level. She had polyuria, nocturia, and polydipsia for 3 years. The polydipsia was attributed to psychogenic cause in the context of ongoing serious personal and familial psychosocial stressors. She had menarche at 13 years of

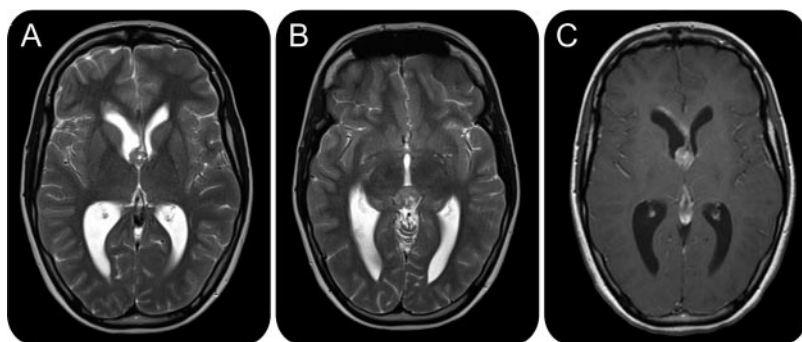
age but for the previous 2 years she had had irregular menstrual cycles, occurring once or twice a year. Her appetite was preserved and her weight was stable within 6 months preceding the diagnosis (54.5–55.7 kg). Her general physical as well as the neurologic examinations were normal. The above features were suspicious for an intracranial mass lesion around hypothalamic/suprasellar region. Her evaluation revealed central diabetes insipidus (DI) based on the history, low urine specific gravity (1.002–1.004), and high urine output (>5 mL/kg/hour). Urine osmolality was 51 mOsm/kg, which increased to 251 mOsm/kg after starting oral desmopressin. Follicular stimulating hormone and luteinizing hormone levels were low; prolactin, insulin-like growth factor, thyroid hormone, and cortisol levels were normal. Her pregnancy test was negative. MRI of the brain showed an intra-axial hypothalamic mass with ependymal extension to the right lateral ventricle involving the body and right frontal horn. There was a second mass in the pineal region. Both the masses enhanced intensely and were hypointense on T2-weighted images, suggesting a radiologic diagnosis of germinoma (figure 1). Spine MRI did not reveal any metastases. There was evidence of early onset acute obstructive hydrocephalus. Serum α -fetoprotein (AFP) and β -human chorionic gonadotrophin (β -HCG) were within normal limits. She underwent an endoscopic intraventricular tumor biopsy which confirmed the diagnosis of germinoma. CSF analysis for tumor staging was withheld owing to hydrocephalus. In view of midline tumors she was presumably considered to have CSF+ disease and treated with craniospinal irradiation (CSI) without adjunctive chemotherapy. She got CSI plus posterior fossa boost with a total dose of 4,500 cGy.

At 1-year follow-up she was completely headache free. The polyuria and polydipsia resolved with desmopressin but menstrual cycles did not completely normalize. Follow-up MRI after 9 months showed complete resolution of the tumor masses (figure 2).

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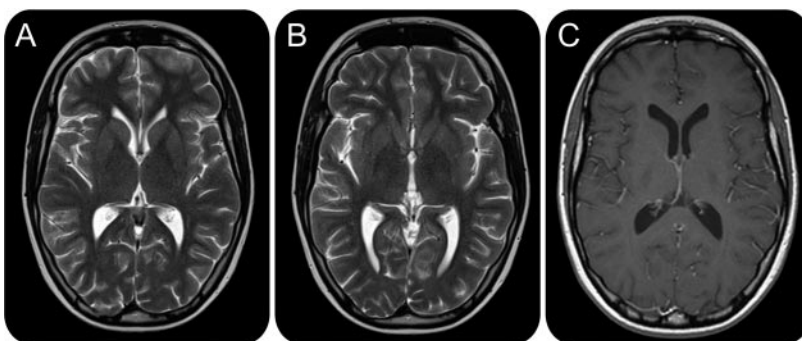
Figure 1 MRI brain (preradiotherapy)



Brain MRI showing (A, B) hypointense mass lesion on T2-weighted image in the hypothalamic and pineal region respectively with early hydrocephalus and (C) intensely enhancing masses on postcontrast T1-weighted image with ependymal extension to the right lateral ventricle involving right frontal horn.

DISCUSSION Intracranial germinoma constitutes 50% to 60% of CNS germ cell tumors (CNSGCT), accounting for 0.5% to 2.0% of all primary intracranial tumors.¹ There is considerable variation in the geographic incidence of intracranial GCT; it is 5–8 times more common in Japan and the far east compared to the western countries.² CNSGCT occurs mainly in children and young adults with a peak age at onset between 10 and 18 years. Overall, male patients are affected more than female patients. WHO classifies CNSGCT into pure germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma, and mixed germ cell tumor.³ CNSGCT arises from the primordial germ cells. These cells appear in the yolk sac wall by the third gestational week and migrate into the genital ridge by the sixth gestational week. If migration of these primordial germ cells is disrupted, some cells may migrate to the ectopic sites (retroperitoneum, mediastinum, or diencephalon) where they can develop into extragonadal GCT.⁴

Figure 2 MRI brain (postradiotherapy)



Follow-up MRI at 9 months post-treatment showing complete resolution of the hypothalamic, pineal masses and hydrocephalus on T2-weighted images (A, B) and no abnormal contrast enhancement in postcontrast T1-weighted image (C).

Germinoma usually occurs along the midline of the body, common locations being the pineal and the suprasellar regions, but can also develop in the basal ganglia region. Tumor cells can seed within the ventricular cavity and the CSF and drop metastases have been described in the spinal cord.⁵ CSF examination and MRI of the spinal cord are needed for appropriate staging of the disease. At the time of diagnosis, 2%–18% of the intracranial germinomas show bifocal distribution with simultaneous pineal and suprasellar manifestations. It remains unclear whether the bifocal tumors result from simultaneous tumor development or represent metastatic disease.⁶

There is a definite relationship between the clinical presentation and tumor location in cases of germinoma. Lesions in the pineal region can obstruct the cerebral aqueduct and cause hydrocephalus with features of raised intracranial pressure (ICP) as the first presenting symptom; they can also present with Parinaud syndrome.⁷ Tumors involving the suprasellar region usually present with hypothalamic–pituitary axis dysfunction such as DI, delayed growth, menstrual irregularities, hypogonadism, or precocious puberty. Patients may also have visual disturbances due to compression of the visual pathways. Interestingly, patients with bifocal germinoma tend to present with symptoms associated with the suprasellar mass initially.⁶ The central endocrinopathy associated with suprasellar GCT is thought to be a consequence of direct pressure by the tumor on the critical hypothalamic areas. These endocrine symptoms tend to occur sooner than a similar sized mass in the pineal region. Additionally, in patients with bifocal disease, the suprasellar mass is frequently the larger of the 2 mass lesions in children.⁶ Thus the diagnosis may be missed if this possibility is not considered as headache and features of raised ICP may be a late manifestation.

The role of protein markers such as β -HCG and AFP that can be measured in the serum or more preferably in the CSF plays an important part in the diagnosis of CNSGCT.³ Yolk sac tumor secretes AFP and choriocarcinoma secretes β -HCG. Embryonal carcinoma usually does not secrete tumor markers but it occurs with other GCT-like yolk sac tumors and is considered as a mixed GCT.⁸ Pure germinomas do not secrete tumor markers. Ancillary tests with typical neuroimaging findings can aid in the diagnosis of CNSGCT without the need for performing brain biopsy.

Intracranial germinoma is considered as a highly curable brain tumor. Radiotherapy is the standard modality of treatment in such patients. With an irradiation dose of 4,000–5,000 cGy, long-term survival is achieved in more than 90% of patients.⁹ Metastatic

intracranial germinoma requires simultaneous radiation to the craniospinal axis.⁶ The side effects of CSI, like neurocognitive deficits, pituitary dysfunction, and secondary malignancies, are of real concern, particularly for younger patients. In order to minimize these, combined modality therapy using cisplatin-based chemotherapy regimens with reduced volume and dose irradiation have shown promising results, showing only 9%–14% local failure rate and a salvage rate of over 50%.¹⁰

There were a number of distractors in the clinical history of this case. Headaches with positive visual phenomena could have been interpreted as migraine with aura. However, our patient had several features which were atypical for migraine, such as bilateral location of the headache, persistent daily headache from the onset, and early morning severe headaches associated with vomiting.

The polydipsia and polyuria were thought to be of psychogenic etiology because there were serious psychosocial issues in the family though the urine specific gravity was clearly low. The differential diagnosis of polydipsia and polyuria should exclude diabetes mellitus and salt-losing nephropathy from end-stage renal disease. In absence of those disorders, one should consider primary polydipsia/psychogenic polydipsia, central DI, and nephrogenic DI. The above disorders can be differentiated based on careful history, checking serum sodium and urine osmolality, performing water deprivation test, and noting the response to exogenous antidiuretic hormone (ADH). In central DI, serum sodium is normal to high with low urine osmolality, and the urine does not become concentrated despite excessively concentrated serum after water deprivation. The urine osmolality increases by more than 50% in response to exogenous ADH as noted in our patient. Oligomenorrhea soon after menarche in our patient was considered to be within normal limits. The combination of new onset headache along with the history of DI and oligomenorrhea pointed to the possibility of intracranial tumor in the suprasellar/hypothalamic region. Endocrine abnormalities and visual field defects are common initial features of pediatric sellar/suprasellar masses. These symptoms may antedate

headache and should be thoroughly investigated to look for abnormalities of the hypothalamic-pituitary-gonadal axis. Intracranial germinomas are exquisitely radiosensitive and chemosensitive and thus are highly curable. New therapeutic strategies are focusing on dose reduction of therapy (radiation and chemotherapy) while still achieving the same cure rates we currently experience.

AUTHOR CONTRIBUTIONS

Dr. Ghosh collected and organized the data and wrote the first manuscript (including the first draft). Dr. Mitra conceptualized the study. Dr. Tekautz and Dr. Mitra verified the results and revised the manuscript at all stages.

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