

Primary skull-based yolk-sac tumour: case report and review of central nervous system germ cell tumours

Raman Verma · Shawn Malone · Christina Canil · Gerard Jansen · Howard Lesiuk

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Abstract Primary intra-cranial germ-cell tumours (GCT) are rare and it is important to differentiate them histologically as their prognosis and treatment is quite different. Moreover, highly malignant non-germinomatous GCT (NG GCT) comprise a small portion of these tumours with limited data available on appropriate treatment approaches. We present the case of a 22-year-old male with a unique primary skull-based yolk-sac subtype NG GCT with a literature review of current treatment options. To our knowledge, there have not been any previously published

reports of a primary yolk-sac tumour arising from the petrous apex.

Keywords Germ cell tumour · Yolk-sac tumour · Endodermal sinus tumour · Intracranial

Case presentation

A 22-year-old male presented to emergency with a headache and a new dilated right pupil. History was relevant for a mild head injury while snowboarding a few days prior while the past medical and surgical histories were non-contributory. Other than signs of a partial right third nerve palsy, the physical exam was unremarkable. CT scan of the head showed a well-circumscribed hyperdense enhancing lesion at the right petrous apex with mild mass-effect on the adjacent brainstem and no hydrocephalus. The imaging was interpreted as “most consistent with a meningioma...and a cranial nerve schwannoma less likely.” It was not felt to be at all consistent with a giant aneurysm and a subsequent CT-angiogram confirmed this to be true (Fig. 1). In light of a putative diagnosis of skull-based meningioma, dexamethasone was started and at the patient’s request, he was discharged to attend an important family gathering.

Unfortunately, his neurological signs and symptoms rapidly progressed over the following 7 days and he returned to emergency with complete right third nerve palsy with a fixed and dilated pupil. This was followed by progressive headaches and right fifth and seventh cranial nerve deficits. Further imaging with gadolinium(Gd)-enhanced MRI again confirmed previous CT findings (Fig. 2a and b) of a mass arising from the right petrous apex and compressing the adjacent brainstem and right

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R. Verma (✉)
Department of Diagnostic Imaging, The Ottawa Hospital,
Civic Campus, 1053 Carling Ave, Ottawa,
ON K1Y 4E9, Canada
e-mail: ramanverma@gmail.com

S. Malone
Department of Radiation Oncology, The Ottawa Hospital,
TOH Regional Cancer Centre 501 Smyth Rd, Ottawa,
ON K1H 8L6, Canada

C. Canil
Department of Medical Oncology, The Ottawa Hospital,
TOH Regional Cancer Centre 501 Smyth Rd, Ottawa,
ON K1H 8L6, Canada

G. Jansen
Department of Anatomical Pathology, The Ottawa Hospital,
TOH Regional Cancer Centre 501 Smyth Rd, Ottawa,
ON K1H 8L6, Canada

H. Lesiuk
Department of Neurosurgery, The Ottawa Hospital,
Civic Campus, 1053 Carling Ave, Ottawa,
ON K1Y 4E9, Canada

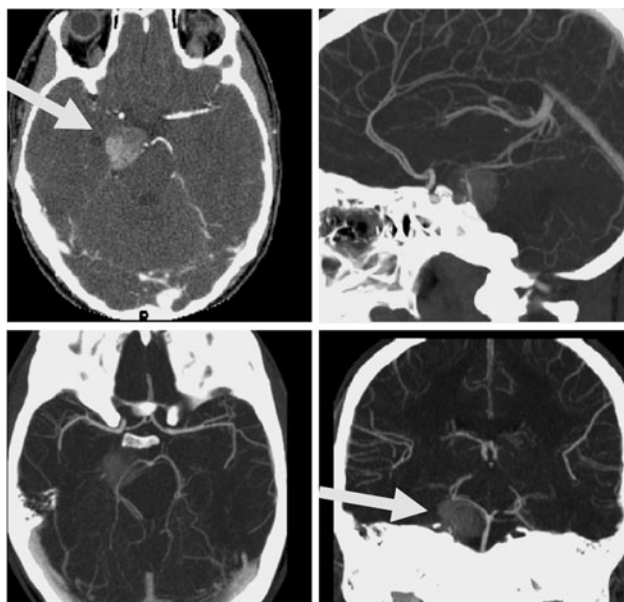


Fig. 1 Axial CT with contrast (*top left*) with sagittal, axial and coronal MIP reconstructions demonstrate an enhancing right CPA mass without evidence of giant aneurysm

temporal lobes. A minimal dural tail was also noted consistent with an extra-axial lesion such as a meningioma. No large vessel was identified supplying the mass.

The patient was brought to the operating room on the second day of admission having received pre-operative dexamethasone. The patient was positioned supine with padding under the right shoulder and head turned to the left. A fronto-temporal craniotomy was turned. However, despite intra-operative mannitol, when the dura was opened the brain was tense and bulging out of the opening. This persisted to a significant degree despite a number of intra-operative manoeuvres including head elevation, hyperventilation and additional diuretics. The neurosurgical

team felt that excessive and destructive brain retraction would be necessary to proceed and the procedure was therefore terminated.

Subsequently 2 days later, the patient returned to the operating room having received high dose dexamethasone and intermittent mannitol (0.25 g/kg q6h) pre-operatively. He was placed in a left-side down decubitus position and general anaesthesia was induced with barbiturate and narcotic. A lumbar drain was placed for intra-operative CSF drainage. With these modifications, adequate brain relaxation was obtained and a slow and tedious internal debulking of a vascular tumour ensued. Grossly the tumour was noted to be quite adherent and infiltrating the surrounding neural structures, particularly the brain-stem and encasing the basilar artery. As a result, a thin rim of residual tumour was left rather than risk damage to these critical structures.

Histopathological examination demonstrated a mostly undifferentiated adenocarcinoma, with a small focus of extracellular hyaline globules, which were reactive to PAS and PAS-diacetate. Primitive epithelial markers were positive (AE1.3 and to a lesser extent, Cam 5.2); however, upon further immunohistochemical staining it showed strong positivity for all tumour cells in alpha-fetoprotein (AFP). Even though Schiller-Duval bodies were negative, considering the strong AFP positivity, the diagnosis of yolk-sac (germ cell) tumour was made (Fig. 3a and b).

Further staging imaging showed no evidence of primary extra-gonadal or metastatic disease in the abdomen, pelvis or thorax. Scrotal ultrasound and evaluation by urology demonstrated no evidence of a testes primary. An MRI of the spine showed no leptomeningeal spread of disease. As a result, the final diagnosis was that of a primary intra-cranial germ cell tumour (GCT), yolk-sac subtype. Since this diagnosis of GCT was not entertained pre-operatively, tumour markers were only available post-resection with

Fig. 2 **a** Pre-treatment axial T1 Gd-enhanced. **b** Pre-treatment coronal T1 fat-sat Gd-enhanced

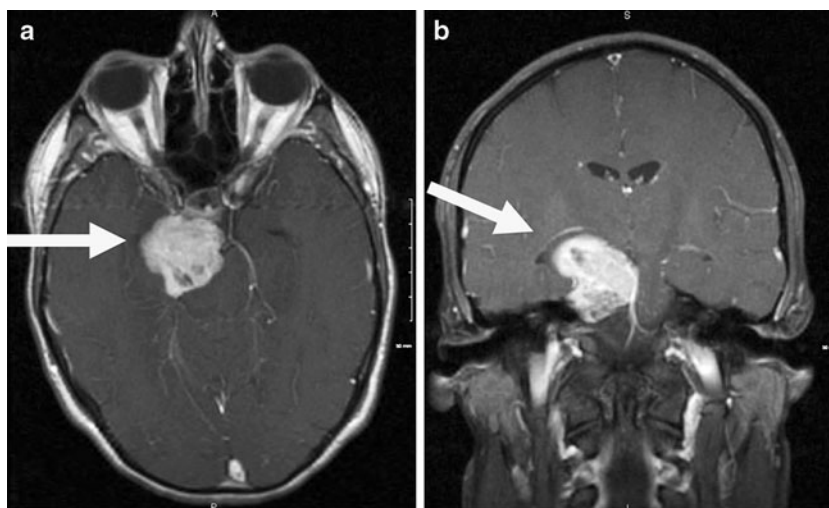
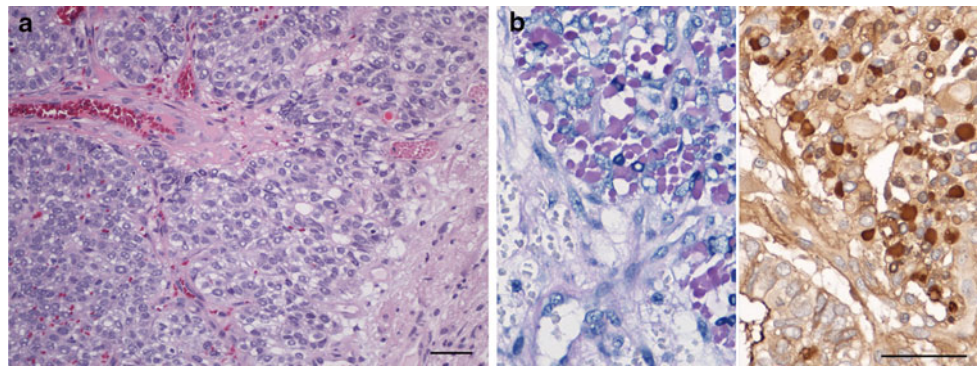


Fig. 3 a H&E stain of tumour (left) bordering on brain tissue (right) with several ill defined tubular structures.

Bar = 50 μ m. **b Left** PAS diastase stain showing small area with hyaline extracellular inclusions. **Right** AFP stain showing same tissue area, with cellular and inclusion positivity for AFP. Bar = 50 μ m



pre-radiation AFP levels of 15,232 mg/l, with a reference range [<9 mg/l]. Beta HCG and LDH levels were normal.

Postoperatively, the patient developed severe right-sided hemiplegia. Two weeks after the initial debulking surgery, he experienced a progressive neurological decline and decrease in level of consciousness (LOC) attributed to increasing edema, haemorrhage into the resection bed and hydrocephalus not readily improved with the insertion of an extraventricular drain (EVD). After a multidisciplinary discussion, a salvage operation was undertaken to evacuate the haemorrhage and undertake a more aggressive radical debulking to relieve mass effect.

Postoperative course was complicated by pneumonia and bilateral pulmonary emboli with worsening LOC and respiratory status requiring ventilatory support. The patient was deemed unstable for chemotherapy, and after consultation with Medical Oncology and accounting for worsening clinical status, it was determined that to proceed with initial systemic chemotherapy may result in increased morbidity and mortality. As a result, emergency radiotherapy was initiated. Utilizing 3D conformal radiotherapy techniques the patient received 5000 cGy in 25 fractions over 5 weeks. Over the course of radiotherapy the patient showed significant tumour response evident by decreasing AFP levels and improvement in LOC and respiratory status allowing for extubation. At the end of the patient's radiation therapy, his AFP decreased from a pre-radiation level of 15232 to 349 μ g/l. The patient tolerated the treatment well and experienced no immediate complications other than alopecia and skin erythema.

Four weeks post radiotherapy, systemic chemotherapy was initiated with four cycles of Vinblastine (0.11 mg/kg/cycle), Cisplatin (20 mg/m²/cycle) and Ifosfamide (1500 mg/m²/cycle). Following completion of his first cycle, the patient experienced intractable seizures secondary to shunt failure causing hydrocephalus requiring intubation and short ICU admission. Aside from fatigue and an episode of febrile neutropenia successfully treated with antibiotics, the patient experienced no other immediate complications and tolerated his chemotherapy well.



Fig. 4 Axial T1 Gd enhanced 5 months post-completion of medical and radiotherapy demonstrates interval improvement

Most recent restaging workup 15 months post-resection and 7 months post-completion of radiation and chemotherapy demonstrates no radiological evidence of recurrence or metastatic disease with an AFP of 5 μ g/l, well within the normal range (Figs. 4, 5). The patient has completed inpatient rehabilitation and is now attending outpatient sessions with only mild residual deficits of mild right motor paresis and spasticity without cognitive deficits or hearing problems.

Literature review

Germ-cell tumors (GCT) are most commonly found primarily in the testes or ovaries. The central nervous system (CNS) is one of several extragonadal sites of presentation; however, intracranial GCTs are quite rare accounting for only 1% of all brain tumours [1]. The incidence of the various germ cell subtypes vary according to age, but some studies indicate that non-germinomatous germ-cell tumours

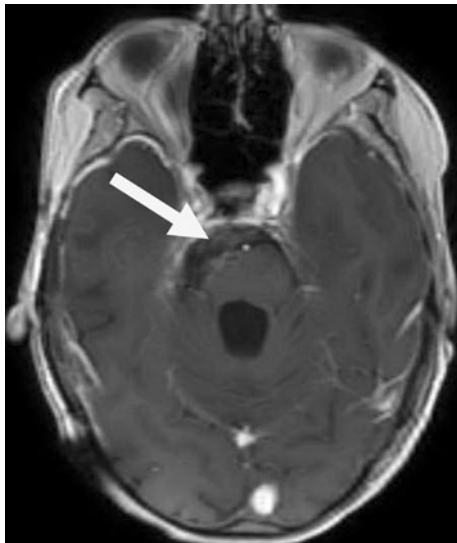


Fig. 5 Axial T1 Gd enhanced 9 months post-treatment. Further interval improvement with no significant residual enhancing mass noted

(NGGCT) make up 40% of all intra-cranial GCT [1, 2] (Table 1).

In a recent Japanese study of 153 histologically verified CNS germ-cell tumours, the approximate occurrence of the various subtypes were germinomas (39%), teratomas (20%), embryonal carcinoma (3%), choriocarcinoma (2%), yolk-sac tumours (2%) and mixed tumours (32%) [5].

Nearly all intracranial GCT originate along the axis from the suprasellar region to the pineal gland with the pineal area being most common [2]. A review of the literature did not yield any recent previously published reports of a primary yolk-sac tumor arising from the petrous apex. Case reports have described primary tumors of this type in the spine and cerebellum as well as the paranasal sinuses [6–8]. Jennings et al. [2] demonstrated that germinomas tend to arise in the suprasellar region (57%) whereas NGGCT are more common in the pineal region (68%). It is important to differentiate GCT from a NGGCT as these different entities have a great variation in prognosis with the latter demonstrating very poor survival rates [5, 9, 10].

There are very few prospective studies available and limited retrospective studies on intracranial germ cell

Table 1 Classification of germinomatous and non-germinomatous GCTs [3]

Germ cell tumours
Germinoma
Non-germinoma
Teratoma
Embryonal carcinoma
Choriocarcinoma
Yolk-sac tumour
Mixed-tumour

tumours secondary to the limited number of patients. As a result, there is no consensus regarding the specific details surrounding the multimodality approach to treatment including surgery, radiotherapy and chemotherapy [4, 11].

Pathology

Histologically, these tumours are identical to those found in the testes and ovaries, composed of cells resembling various embryogenic stages of development [1, 10]. Yolk-sac tumours can be subdivided into a variety of patterns with a reticular/microcystic growth pattern (80% of cases) being most common. Other patterns include poly-vesicular vitelline, solid, papillary, spindle cell, enteric and hepatoid growth patterns. Diagnostic features of yolk-sac tumours include Schiller-Duval bodies present in approximately 70% of cases, as well as cytoplasmic and extra-cellular eosinophilic globules. AFP stains the tumour cells, and often also the hyaline globules [10]. In addition, they are composed of primitive epithelial cells and have a reticular pattern of loose meshwork or compact sheets [1, 2, 10].

Imaging

There have only been a few reports on the imaging findings of intra-cranial germ cell tumours. Fujimaki et al. [12] analyzed the CT and MRI features of 73 histologically proven IC GCT and demonstrated a variety of imaging features not specific to a histological diagnosis. The appearance of yolk-sac tumours was irregular. Pre and post-gadolinium MRI is the imaging modality of choice with a hypointense/isointense lesion on T1 and an isointense or slightly hyperintense lesion on T2. The lesion usually enhances heterogeneously however these findings are not specific for yolk-sac tumours [12, 13]. Some reports describe lesions that are irregular and isointense, hypointense and or hyperintense to gray matter [10].

There are no features pathognomonic for NG GCTs; however, MRI is quite useful in developing a differential diagnosis as well as detecting various components and anatomical relationships to aid in target volumes for radiotherapy as well as surgical planning. It is impossible to ascertain a diagnosis based solely on the imaging findings alone [1, 12].

Discussion

The prognosis of IC NG GCT has been established to be quite poor. Matsutani et al. described 3-year survivals of 27% for pure choriocarcinoma, endodermal sinus or

embryonal carcinomas; 9% for mixed tumours; as opposed to 3 year survival of 70% for germinomas [5]. Sawamura et al. analyzed [9] 111 patients and determined that IC GCTs which included a highly malignant component such as embryonal carcinoma, yolk-sac tumour or teratoma exhibited poor survival of 38% 5-year and 25% 10-year survival rates. Moreover, yolk-sac tumours specifically had the worst prognosis with 25% 5-year and 0% 10-year survival in four patients.

Limited studies have been performed regarding the management of IC GCTs however the general consensus is that multimodality approach is imperative. Robertson et al. described a multimodal “sandwich” therapy consisting of neoadjuvant chemotherapy, radiotherapy and then further chemotherapy after surgical debulking as an effective approach shown to improve outcome [5]. They described 18 newly diagnosed patients with proven intra-cranial NGGCT without evidence of metastatic disease and showed four year event-free and total survival rates of 67 and 74%, respectively [14].

Intra-cranial non-germinomatous GCT are much less radio-sensitive and demonstrate long-term poor survival when compared to intra-cranial germinomas [15]. Surgical debulking has long been advocated in NG GCT to reduce tumour mass and increase curative potential of radiotherapy and or chemotherapy [1, 16]. However, specific treatment of NG GCT is much less clear.

Our case illustrates the circumstances of a patient with an intracranial GCT who was medically unstable to consider upfront chemotherapy. The patient had an excellent clinical, marker and radiologic response to radiation allowing the safe integration of aggressive chemotherapy post radiation.

Wolden et al. [16] examined 48 patients with confirmed or suspected primary IC GCT of which 34 had a pathological diagnosis. In the 10 patients with NG GCT, there were 3 teratomas, 2 choriocarcinomas, 1 embryonal carcinoma and 1 endodermal sinus tumour with 3 mixed tumours. Since these patients covered a 22 year span, some received with or without whole-brain or whole-ventricular irradiation and this resulted in a 5-year disease-free survival of 60%. Routine prophylactic cranio-spinal axis irradiation was not given; however, 50 Gy was recommended for gross involvement and 40 Gy for cytologic spread only. However, this study was limited secondary lack of consistency of dose and field [1, 17].

A more recent study by Haas-Kogan et al. looked at 93 patients of which 16 were NG GCT and 28 had no biopsy and demonstrated 5-year progression free survival (PFS) of 60% and overall survival (OS) of 68%. However, as the author stated, there is much controversy in the focal radiation fields as many North American studies have not delineated if the fields included only the targeted tumour or

the ventricular system for example. In this study, most patients again received 50–54 Gy [17]. In our institution, only local field radiation is utilized as prophylactic cranio-spinal irradiation causes marrow suppression potentially limiting systemic therapy.

General consensus now exists that chemotherapy should be part of treatment for IC NG GCTs and results in improved survival [8, 16, 17]. Platinum-based regimens are based largely on the experience of systemic non-CNS GCT because of the embryological and histological similarities [18]. Radiation therapy alone cannot control tumour progression systemically. In general, chemotherapy is not effective treatment of intracranial malignancies, as these drugs do not usually cross the blood brain barrier. However, Cisplatin may be an exception and patients with non-intracranial germ cell tumours and brain metastases have demonstrated intracranial responses with chemotherapy alone [19].

Conclusion

Intra-cranial non-germinomatous GCTs are rare and require a tailored approach to their treatment algorithm. These patients are often young with minimal comorbidities, and given the potentially poor outcomes, an aggressive multi-modality approach with surgery, radiation and chemotherapy is recommended. Our case presents a unique location for a primary yolk-sac tumor, one not previously described in literature. Moreover, in a patient not sufficiently stable for systemic chemotherapy initially, we demonstrated significant clinical and biochemical improvement with radiotherapy. Despite the grave prognosis, combined therapy has to date contributed to significant response.

Further multicenter studies are required and are underway to help further delineate treatment approaches and better appreciation of prognosis and survival. Ongoing phase II and phase III trials for these IC GCTs are proceeding including those with the International CNS Germ Cell Tumour study group [20, 21].

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