Case Report

Mediastinal metastases from a primary immature teratoma of the CNS ☆

Sultan M. Zain, MPH[a],*, Kanish Mirchia, MD[b], Kristyn Galbraith, MD[b,c], Michael A. Galgano, MD[d], Mijung Lee, MD[e], Timothy E. Richardson, DO, PhD[b,f,g], Kavya Mirchia, MD[h]

[a] College of Medicine, State University of New York, Upstate Medical University, Syracuse, NY 13210, USA
[b] Department of Pathology, State University of New York, Upstate Medical University, Syracuse, NY 13210, USA
[c] Department of Pathology, New York University Langone Health, New York City, NY 10016, USA
[d] Department of Neurosurgery, State University of New York, Upstate Medical University, Syracuse, NY 13210, USA
[e] Department of Internal Medicine, Division of Hematology Oncology, State University of New York, Upstate Medical University, Syracuse, NY 13210, USA
[f] Department of Pathology and Laboratory Medicine, University of Texas Health San Antonio, San Antonio, TX 78229, USA
[g] Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases, University of Texas Health San Antonio, San Antonio, TX 78229, USA
[h] Department of Radiology, State University of New York, Upstate Medical University, Syracuse, NY 13210, USA

ABSTRACT

Primary intracranial germ cell tumors are rare, occurring more frequently in children and young adults in midline locations of the brain. Teratomas are an uncommon variant of germ cell neoplasm, although they account for a high proportion of fetal brain tumors. Here, we report a 27-year-old male who presented with a heterogeneously enhancing lesion in the left thalamus, without evidence of systemic disease. Histologic and immunohistochemical analysis were consistent with immature teratoma; next-generation sequencing was negative for targetable molecular alterations. The patient received chemotherapy and radiotherapy post-excision. Following the initial resection, ventriculoperitoneal shunt placement was performed due to left temporal horn entrapment. Nine months later, imaging revealed mediastinal and hilar adenopathy as well as pleural disease, with encasement and compression of pulmonary vasculature, and multiple, bilateral pulmonary nodules. Fine needle aspiration showed malignant cells with an immunohistochemical profile similar to the original tumor, consistent with metastases. Though germ cell tumors are known to spread via cerebrospinal fluid or blood, metastasis outside of the CNS from a primary intracranial germ

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* Corresponding author.
E-mail address: ZainS@upstate.edu (S.M. Zain).
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cell tumor is a rare complication. Spread via ventriculoperitoneal shunt, which may have occurred in the present case, has also rarely been observed.

Introduction

Primary intracranial germ cell tumors (GCTs) are quite rare, especially in the adult population, comprising approximately 2% to 3% of all pediatric brain tumors with 85% of them occurring before the age of 20 [1]. There are 2 major types of GCTs, including germinomas and nongerminomatous GCTs, with teratomas usually delineated as a separate category [2]. Teratomas can be further divided into mature and immature subtypes, with mature teratomas being composed of fully differentiated tissue containing elements from ectoderm, mesoderm, and endoderm whereas immature teratomas have elements of less differentiated tissues [2]. Central nervous system (CNS) teratomas, which comprise only a fraction of already rare CNS GCTs, are even rarer with one study finding that they composed less than 0.2% of CNS tumors at a particular institution [3]. While peak incidence of GCTs overall is between 10 and 19 years of age, incidence varies by tumor type. Teratomas are more common in the neonatal period whereas germinomas and nongerminomatous GCTs are more prevalent in older children/adolescents [4].

While GCTs are known to spread via the cerebrospinal fluid (CSF) [5,6] and hematogenous route, metastasis outside of the CNS from a primary intracranial germ cell tumor is a rare complication [7,8]. Given that CSF is a source of spread, metastasis via a ventriculoperitoneal (VP) shunt, while rare, has also been observed in multiple cases [9,10]. Therefore, this case, along with presentation of a rare tumor in an atypical age group, represents a strikingly uncommon distant metastasis with a primary CNS germ cell tumor.

Case presentation

A young male in his twenties with no significant past medical history presented to an outside hospital with complaints of a severe headache, nausea, dizziness, memory difficulty, and blurry vision lasting 5 days. A computed tomography (CT) scan of the head there revealed a brain mass, and he was transferred to our facility where he underwent further workup and received more comprehensive imaging. His vitals at presentation were largely unremarkable. On examination, he presented with a right homonymous hemianopsia and impaired recall, remembering zero of 3 words after 2 minutes. He was without any brain stem, motor, or sensory deficits at presentation though did demonstrate mild right upper extremity weakness later in his hospital course. Neurology and neurosurgery were both consulted.

Magnetic resonance imaging (MRI) of the brain with and without contrast revealed a heterogeneously enhancing lesion in the left thalamus, displacing the left thalamus ante-

riorly and the left lateral ventricle laterally (Fig. 1A). Vasogenic edema was noted in the left parietal lobe, dorsal aspect of the left basal ganglia, as well as midbrain (Fig. 1B). Diffusion tensor imaging and fiber tractography demonstrated displacement of left internal capsule (Fig. 1C). There was no evidence for systemic involvement, as metastatic workup was negative including further imaging of the spine and thorax. Dexamethasone and levetiracetam were initiated for vasogenic edema management and seizure prophylaxis, respectively. After discussion with the patient and his family, the decision was made to pursue surgical intervention, and so the patient underwent a left stereotactic tumor biopsy that was tolerated well.

Microscopic sections demonstrated a biphasic neoplasm composed of hypercellular fragments of hyperchromatic cells forming epithelial glands with intervening mesenchymal elements, including focal mature cartilage and tissue of sarcomatoid differentiation (Fig. 2A and B). There were frequent atypical mitotic figures (Fig. 2A) throughout both tumor components as well as areas of focal necrosis. The glands were strongly positive for keratin (Fig. 2C) and focally positive for EMA. The mesenchymal elements were positive for vimentin (Fig. 2D). The tumor cells were also widely positive for CD99 with patchy positivity for NSE, neurofilament, and nestin, and negative for GFAP, synaptophysin, and placental alkaline phosphatase. Germ cell markers, including SALL4 (Fig. 2E), Oct3/4 (Fig. 2F), CD117, and alpha-fetoprotein (AFP) (Fig. 2G) were focally positive. The Ki-67 proliferation index was high throughout the tumor (Fig. 2H). These results were consistent with an immature (malignant) teratoma. A Foundation One study was negative for any targetable molecular alterations.

A left parieto-occipital craniotomy was performed and resection of tumor was done without any complications. Following the initial resection, a VP shunt was placed due to left temporal horn entrapment. The patient also received chemotherapy and radiotherapy post-excision. Nine months later, he was readmitted for shortness of breath. Computed tomography angiography of the thorax revealed mediastinal and hilar adenopathy as well as pleural disease (Fig. 3A), with encasement and compression of the pulmonary vasculature, and multiple, bilateral pulmonary nodules (Fig. 3B).

Fine needle aspiration of mediastinal lymph nodes demonstrated single and loosely cohesive clusters of malignant cells with a similar immunohistochemical profile to that of the primary tumor (Fig. 4A-C). The oncology team thus proceeded with a chemotherapy regimen.

Discussion

Teratomas, as discussed before, are a rare type of GCT that tends to occur more frequently in neonates. Prognosis of ter-
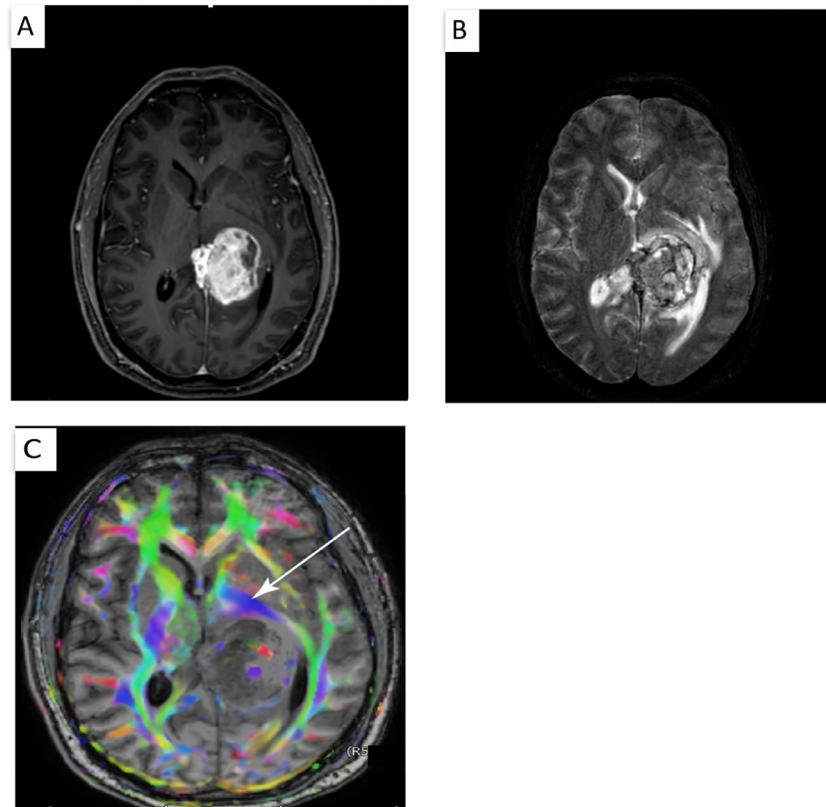
Fig. 1 – Axial T1-weighted 3D post-gadolinium image showing large heterogeneously enhancing tumor in the region of left thalamus causing lateral displacement of the left lateral ventricle and anterior displacement of the left thalamus (A). Axial 3D T2-weighted image showing heterogeneous tumor with surrounding vasogenic edema (B). Diffusion tensor imaging (DTI) and fiber tractography showing displacement of left internal capsule (C, white arrow).

atomas is varied based on type, with mature teratomas being associated with a better prognosis [4]. Immature teratomas, being composed of more primitive tissue, have a greater potential for malignant transformation and not surprisingly have lower survival rates within the 50%-70% range [4,11]. Common primary locations of teratomas include the sacrococcygeal region as well as the abdomen; only 3.5% of teratomas are found in the CNS [11]. Within the CNS itself, teratomas, like other GCTs, have a predilection for the pineal and suprasellar regions [2,3]. Interestingly, pineal area tumors are more common in males whereas suprasellar tumors are more common in females [2]. Other locations of occurrence include the fourth ventricle, basal ganglia, and thalamus, as in our patient [12].

Clinically, the presentation can vary based on the location of the tumor but common symptoms can include headache, ataxia, and dysmetria if there is cerebellar involvement, diabetes insipidus if there is suprasellar involvement, other hormonal disruption given hypothalamic/pituitary involvement or direct tumor secretion, visual abnormalities if the optic chasm is involved, and Parinaud syndrome in the case of pineal involvement or related hydrocephalus [13]. Facial paresis, hemiparesis, and other focal symptoms are also possible given involvement in certain regions [12].

Delayed diagnosis has been noted to be more pronounced in pediatric brain tumors versus other malignancies; this re-

lationship holds true for intracranial GCTs. While this observation cannot be definitively explained, this delay can be attributed to a number of potential factors, such as the latent nature of some of these tumors, the occasionally equivocal appearance of subtle imaging findings, as well as the early age of onset [14]. Serum/CSF tumor markers can be measured to aid in diagnosis; yolk sac tumors secrete AFP, choriocarcinomas secrete human chorionic gonadotrophic hormone (HCG), and teratomas can secrete both AFP and HcG. Germinomas are associated with both HCG and placental alkaline phosphatase. Some common immunohistochemical tumor markers for germinomas include c-kit and OCT3/4. Embryonal carcinomas, which are generally not associated with any serum tumor marker, stain strongly for CD30 and CK AE1/3 [12]. Given positive tumor markers, clinical features, and imaging findings, a diagnosis can be made without biopsy but without definitive tumor markers, biopsy is often required to confirm diagnosis [13].

On CT imaging of teratomas, calcification, cystic components, and/or fat are often noted [15]. On MRI, GCTs are described to be hypo- to isointense on T1W images and hyperintense on T2-weighted (T2W) images; it should be noted though that teratomas cannot always be reliably differentiated from other GCTs on imaging alone, including MRI [3,15,16]. One retrospective study characterizing imaging findings of intracranial teratomas noted, as discussed before, the
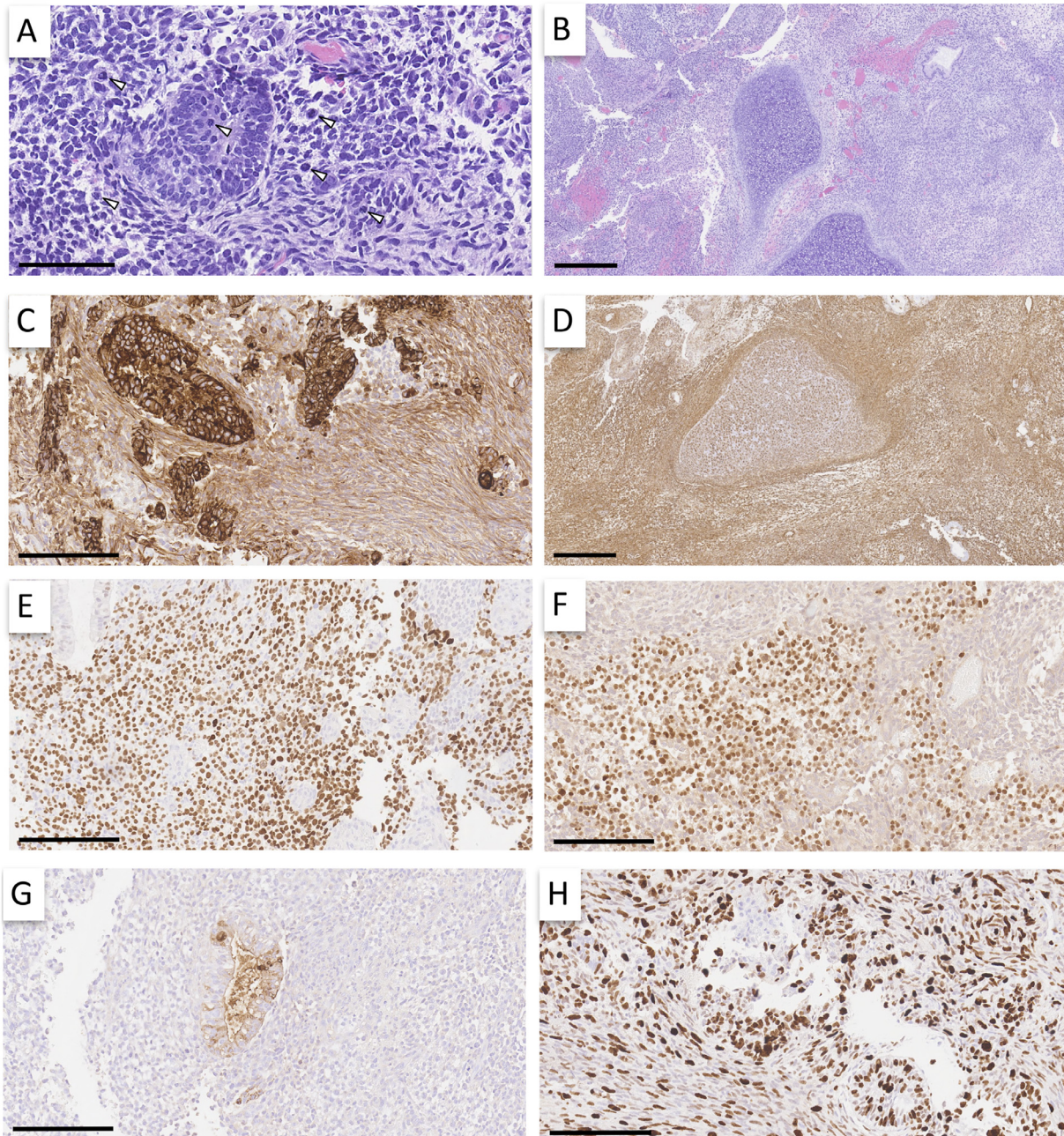
Fig. 2 – Primary thalamic neoplasm. Histology images from Hematoxylin and Eosin (H&E) sections (A-B) demonstrating glandular and cartilaginous differentiation as well as frequent mitotic figures (arrowheads). The glands are strongly positive for keratin (CAM5.2) (C) and the mesenchymal elements are positive for vimentin (D). SALL4 (E) and Oct3/4 (F) staining confirms the germ cell component, AFP shows focal staining in the gland-like component (G), and Ki-67 demonstrates a high proliferative rate (H). Panel A is taken at a total magnification of 400x, scale bar = 100 μm, B & D are taken at a total magnification of 50x, scale bars = 500 μm, C, E, F, G, and H are taken at a total magnification of 200x, scale bars = 200 μm.

predilection of this tumor for midline locations in the brain, such as the pineal, suprasellar, and parasellar regions [17]. Occurrence in the thalamus has been described in the literature, as in our case, but is highly unusual [12,18]. In the aforementioned study, Liu et al. noted that lesions were of mixed intensity on MRI, which was described as being consistent with the heterogenous nature of teratomas. Furthermore, the ma-

jority of mature teratomas were noted to show non-enhanced multilocularity or heterogeneous enhancement of the cyst wall on contrast-enhanced T1-weighted images (T1W) with a minority showing moderate heterogeneous enhancement within the solid portion of the lesion. In contrast, the immature teratomas and teratomas with malignant transformation demonstrated heterogenous, ring-like, intratumoral
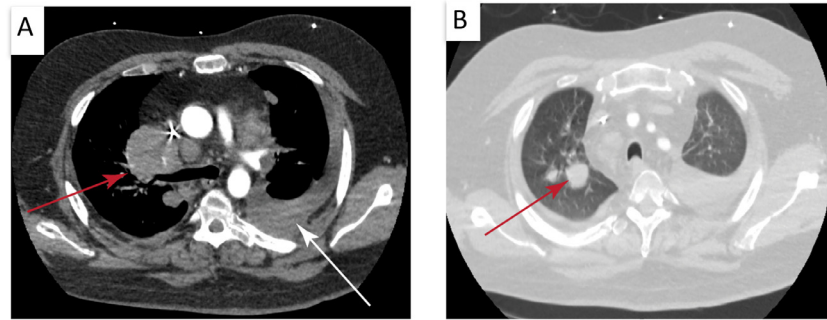
Fig. 3 – Computed tomography angiography (CTA) of the thorax showing enlarged mediastinal and hilar lymph nodes (A, red arrow) and left pleural effusion (A, white arrow). CTA thorax with multiple pulmonary nodules (B, red arrow).
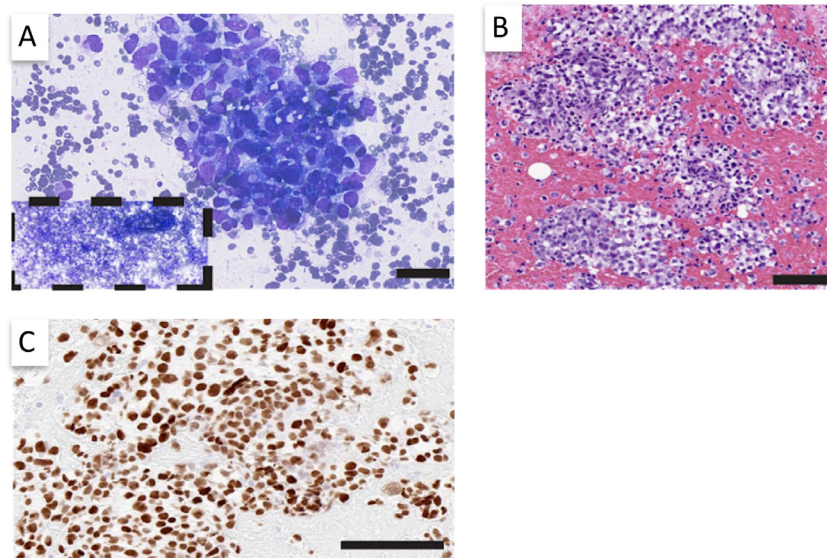

Fig. 4 – Mediastinal lymph node. Fine-needle aspiration demonstrating a few loosely cohesive clusters of malignant cells (A), with similar morphology in the cell block (B), and staining positive for SALL4 (C), confirming metastatic germ cell tumor. Panel A is taken at a total magnification of 400×, scale bar = 50μm (inset at 200×). Panels B & C are taken at a total magnification of 200×, scale bars = 100 μm.

patchy enhancement on T1W images with contrast [17]. Ultimately, it appears as though enhancement of the solid portion of a teratoma is reflective of a more aggressive tumor with malignant potential [3,17].

A definitive treatment algorithm for intracranial teratoma remains elusive. While complete surgical resection of a mature teratoma is likely to be curative due to a relatively low rate of recurrence, the presence of even a small portion of immature or malignant tissue can predispose to recurrence [19]. While adjuvant therapy increases survival in nongerminomatous tumors compared to resection alone [20], it has unfortunately been associated with a phenomenon known as GTS, wherein paradoxical growth of lesion may be encountered during or after therapy [21]. As such, second-look surgery is recommended in those patients whose tumors are unresponsive to adjuvant therapy and regardless of treatment algorithm utilized, close follow-up over time is needed to monitor for recurrence [22].

Conclusion

Intracranial teratomas, being a rare subtype of already rare intracranial GCTs, pose a set of diagnostic and treatment challenges. While clinical history, characteristic imaging features, and pathological markers may help determine a prognosis and treatment plan, histological workup is essentially required for a definitive diagnosis. Furthermore, given the possibility of recurrence as well as phenomena like GTS during or after adjuvant therapy, close follow-up should be maintained post-surgical resection. In our case, a patient with a thalamic immature teratoma removed by surgical resection was found to have developed mediastinal metastases on follow-up. While the spread of GCTs to outside the CNS through the hematogenous route is ultimately rare, the patient's VP shunt was also a potential source of spread, highlighting the need to monitor patients with such shunts carefully.

Ethics approval

This is a retrospective case report not requiring ethics approval.

Patient consent statement

Consent was obtained from patient's family as patient had passed away as of this manuscript's composition.

Authors' contribution

All authors contributed to writing this manuscript. All authors read and approved the final manuscript.

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