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Clinical Study

Management of central nervous system teratoma



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ABSTRACT

Central nervous system (CNS) teratomas are very rare neoplasms that contain tissues derived from all three germ cell layers (endoderm, mesoderm, and ectoderm). Patients with teratomas usually have a good prognosis. Given the paucity of cases in the literature, we present a retrospective review of 15 CNS teratomas treated over a 25 year period at the University of California, San Francisco. We describe the presentation, location, treatment, and adjuvant therapy for these patients, and highlight three unique cases that emphasize the diverse presentation and treatment of these rare tumors.

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1. Introduction

Central nervous system (CNS) teratomas are very rare neoplasms that include mixed and malignant subtypes and account for approximately 0.5–1% of primary adult intracranial tumors. There is a higher frequency in children (~7%) and in countries such as Japan, Korea, and Taiwan (1.8–5% in adults, up to 15% in children) [1]. Teratomas are a subset of nongerminomatous germ cell tumors (that also include embryonal carcinomas, choriocarcinomas, and yolk sac/endodermal sinus tumors), and are unique in that they are composed of tissues derived from all three germ cell layers (endoderm, ectoderm, and mesoderm). In the CNS, they usually arise in midline locations and are more common in the pineal region, suprasellar cistern, basal ganglia, and thalamus [2], with rare examples in other locations such as the temporal lobe [3], cerebellum [4], lateral ventricles [5], or posterior fossa [6,7]. In the spine, they are more often extramedullary [8], and are more often found at thoracolumbar levels [8,9]. Unlike other germ cell tumors, teratomas usually have a good prognosis, with 5 year survival rates ranging from 87 to 100% for mature teratomas [1,10,11] and 33 to 71% for malignant teratomas [1,11].

Given their rarity, there are relatively few studies of CNS teratomas in the literature. Besides the limited case reports of congenital teratomas [12–18], to our knowledge there are only two large case

series, one with 14 pediatric patients with intracranial teratomas [1], and another with 31 patients with intracranial teratomas in South Korea [2]. In this paper, we present a retrospective review of 15 patients with CNS teratomas treated at the University of California, San Francisco, over a 25 year period, from 1982 to 2007.

2. Methods

A retrospective review was performed of all patients undergoing surgery for resection of a teratoma at the University of California, San Francisco (UCSF) between 1982 and 2007. A list of all patients undergoing resection for a brain or spinal tumor was generated from a database containing all operative procedures, and cross-referenced with a pathology database to identify all patients with histopathologically confirmed teratomas. Identifying patient characteristics, including name, diagnosis, and tumor location were prospectively collected in these databases for all consenting patients undergoing neurosurgical evaluation at UCSF; this occurred in accordance with the Committee for Human Research (CHR# H7828-29842-01).

The medical records, radiographic imaging, pathology reports, and operative notes for each of these patients were reviewed. Data collected included patient demographics, preoperative symptoms, surgical approach, tumor location, extent of resection, postoperative symptoms, adjuvant therapy, tumor recurrence, and years of follow-up. Standard pathologic examination (gross and microscopic examination) was previously performed on all tumor spec-

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imens. The diagnosis of teratoma was established by the presence of endodermal, mesodermal, and ectodermal tissues. Immunohistochemical stains were performed if needed to aid in highlighting particular components of the teratoma in a limited sample or to exclude other diagnoses. The typical diagnostic challenge is in excluding components of other germ cell neoplasms (i.e. mixed germ cell tumor), including immature teratoma, yolk sac tumor, germinoma, embryonal carcinoma, and/or choriocarcinoma.

2.1. Illustrative Patient 1

Our first case was a 10-year-old boy with no prior medical history who presented with 2 weeks of headaches, dizziness, emesis, and a generalized tonic-clonic seizure. A ventriculoperitoneal shunt was placed at an outside hospital for treatment of his hydrocephalus (Fig. 1A, B). For definitive treatment of his third ventricular/pineal region mass, a bifrontal craniotomy using a transcallosal approach was performed and a gross total resection was achieved. The patient experienced no postoperative complications and was discharged home neurologically intact 4 days after surgery without any new neurologic deficits.

At the time of surgery, the tumor was noted to be a reddish, irregular semi-solid mass, with areas of hair, calcification, and cyst. Gross examination of the specimen showed a multiloculated cystic mass, composed of skin, hair, hard bony tissue, and filled with tangential material to clear serous fluid. A few separate fragments of tan-brown to red-gray tissue were also present. The gross and microscopic findings were compatible with a mature teratoma.

No microscopic description was provided in the pathology report, and the slides are no longer available for re-review. Five years later, a new pineal region mass with extension along the right ambient cistern and vermis was identified on follow-up MRI. At this time, the patient had no neurologic symptoms, but slight limitation of upgaze bilaterally with convergence-retraction nystagmus was noted. Serum and cerebrospinal fluid (CSF) markers for beta-human chorionic gonadotropin (beta-hCG) and alpha-fetoprotein (AFP) were negative, and the CSF cytology was negative. The patient had an MRI-guided biopsy, which showed a low-grade astrocytoma. Because of its rapid growth, the tumor was treated as an anaplastic astrocytoma and the patient received focal radiotherapy to a total of 54 Gy, with good response.

2.2. Illustrative Patient 2

In this case, a teratoma was identified in a more unusual location. A 52-year-old man was known to have an intracranial mass for 10 years, and was followed at another institution without definitive treatment. He then presented with headaches, nausea, vomiting, dizziness, hyponatremia, and a possible seizure. An imaging study showed a 4 × 3 cm contrast enhancing heterogeneous mass in the left temporal lobe (Fig. 2A–D). At the time of admission, the patient was drowsy but awakened easily to voice, was oriented and briskly followed commands. However, he became increasingly lethargic while awaiting surgery. A craniotomy was performed with subtotal resection of the mass. Postoperatively, the patient's neurologic status deteriorated, and an

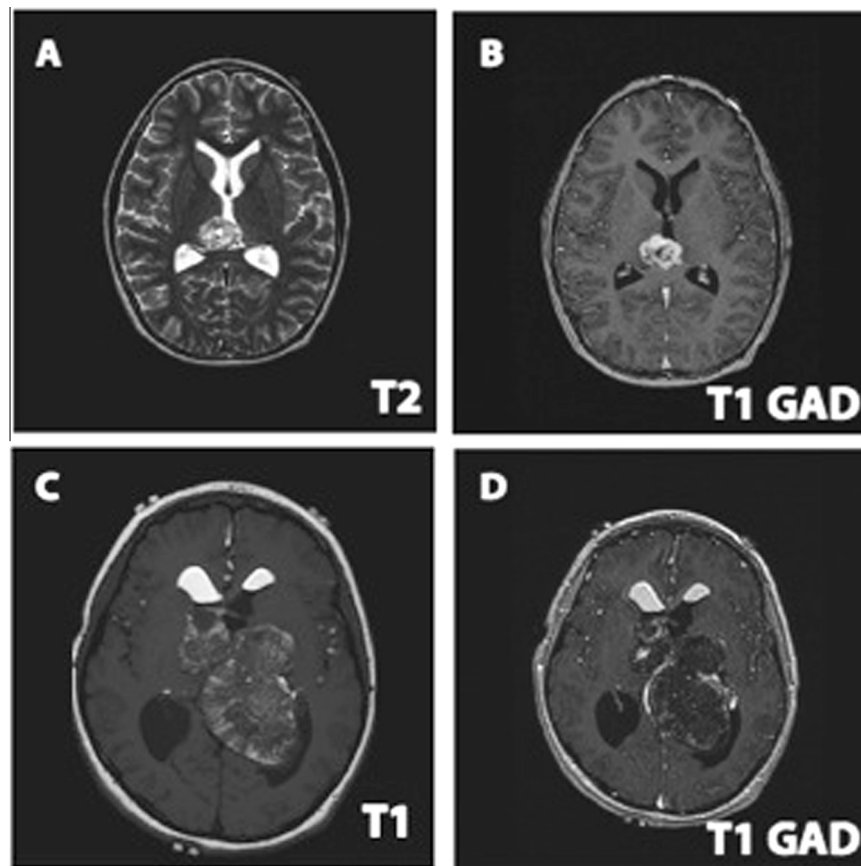


Fig. 1. Teratomas of the pineal region. Axial (A) T2-weighted and (B) T1-weighted with gadolinium (GAD) contrast MRI of a heterogeneous mass of the third ventricular/pineal region (similar in size and location to that described in Illustrative Patient 1, whose images were obtained before 1990 and are no longer available). Axial (C) T1-weighted and (D) T1-weighted with gadolinium contrast MRI showing a multilobular teratoma that is also centered at the third ventricle, but spreads out much further. In this particular case, the teratoma had ruptured into the ventricular system, and the hyper-intense signal in the frontal horns represents dermoid-like material in the ventricles.

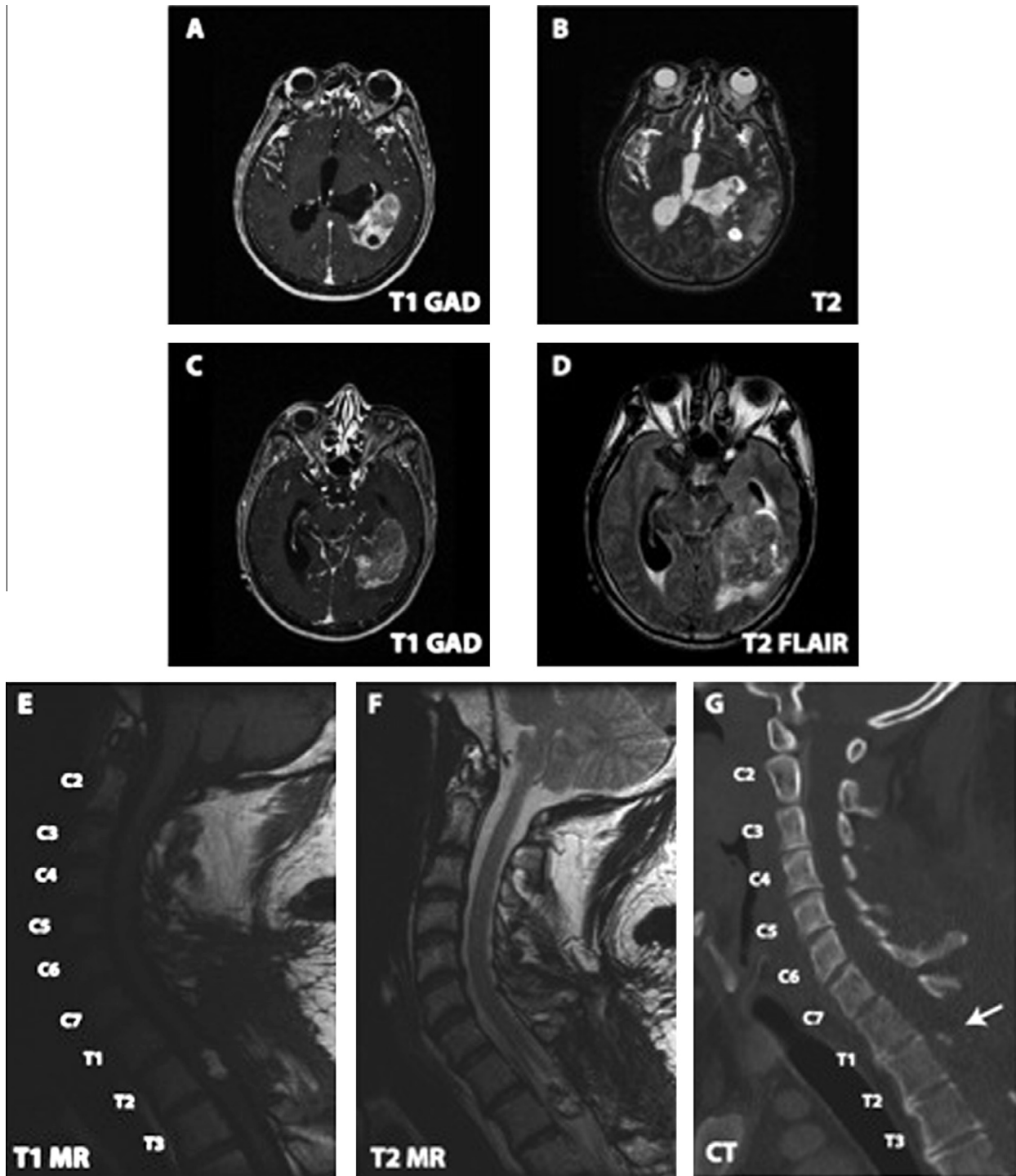


Fig. 2. Teratomas in unusual locations. Axial (A) T1-weighted with gadolinium (GAD) contrast, (B) T2-weighted, (C) T1-weighted with gadolinium contrast and (D) T2-weighted fluid attenuated inversion recovery (FLAIR) MRI of a teratoma located in the temporal lobe (Illustrative Patient 2). Sagittal (E) T1-weighted MRI, (F) T2-weighted MRI and (G) CT scan show a spinal tumor (Illustrative Patient 3) that is hyperintense on T1-weighted (E) and T2-weighted (F) MRI and is calcified on CT scan (G).

external ventricular drain was placed without any improvement. Subsequent imaging studies revealed extensive tumor dissemination throughout the entire spine. No further treatment was given, and the patient died within 3 weeks.

On gross examination, the tumor was heterogeneous, with fragments of pink-tan to yellow soft tissue as well as fragments of red-brown hemorrhagic clot. Histologic examination demonstrated a mixed malignant germ cell tumor composed of teratoma and embryonal carcinoma. The teratomatous component consisted of

mature squamous epithelium, mature bone, foci suggestive of stromal mesenchyme, and malignant squamous epithelium (i.e. squamous cell carcinoma arising in a teratoma). Additionally, a pleomorphic primitive germ cell neoplasm was present, with positive immunostaining for the markers pan-cytokeratin and CD30. Immunohistochemical stains for AFP, placental alkaline phosphatase (PLAP) and hCG were negative. A CD117 stain showed cytoplasmic staining with no appreciable membranous staining. The lack of staining for AFP and PLAP suggest that a yolk sac tumor

Table 1
Demographic and clinical characteristics of intracranial teratomas patients

Age	Sex	Preoperative symptoms	Tumor location	Surgical approach	Postoperative symptoms	Extent of resection	Final pathology	Adjuvant treatment	Follow-up	Recurrence
8.5 mo	F	Respiratory obstruction requiring tracheostomy	Frontal skull base, with extension into posterior pharyngeal space	Bifrontal craniotomy	Transient DI, transient SIADH, right CN VII palsy	GTR	Mature teratoma	None	1 yr	No
22 yr	F	Bitemporal hemianopsia, irregular menses, galactorrhea, weight loss, headaches, nausea	Sellar/suprasellar region	Transsphenoidal	Transient DI	Near GTR	Mixed: mature teratoma and germinoma	XRT/Chemo	10 mo	No
52 yr	M	Headaches, emesis, seizure, lethargy	Left temporal lobe	Left craniotomy	Worsening neurological status	STR	Malignant teratoma	Comfort care	Died	Extensive spread along spinal cord
10 yr	M	Hydrocephalus, seizure, headaches, emesis	Pineal region, third ventricle	Bifrontal craniotomy	None	GTR	Mature teratoma	None prior to recurrence; then XRT	5 yr	Yes (astrocytoma)
4 yr	M	Developmental delay, possible seizures	Third ventricle	Right frontotemporal craniotomy	Transient DI	GTR	Mature teratoma	NA	NA	NA
12 yr	M	Double vision, headaches	Pineal region	Occipital craniotomy	None, delayed panhypopituitarism (>10 yrs later)	GTR	Mixed: adult and immature teratoma, endodermal sinus tumor, embryonal carcinoma, germinoma	XRT/Chemo	14 yrs	No
18 yr	M	Headaches, diplopia, obstructive hydrocephalus, somnolence, bilateral fixed pupils	Pineal region	Suboccipital craniotomy	Persistent poor exam, thalamic infarct, hydrocephalus requiring numerous shunt revisions	GTR	Mixed: adult & immature teratoma, embryonal & yolk sac carcinoma, choriocarcinoma	XRT	NA	NA
10 yr	M	Headaches, vomiting	Pineal region, third ventricle	Right parietal craniotomy	Disease progression, multiple shunt revisions	STR	Mixed: mature teratoma and germinoma	Chemo/XRT	2 yrs	Yes, extensive leptomeningeal carcinomatosis
15 yr	M	Headaches, confusion, GTC seizure	Pineal region, third ventricle	Suboccipital craniotomy	Multiple shunt revisions	GTR	Mixed: mature teratoma and germinoma	Chemo/XRT	3 yrs	No
10 yr	M	Hydrocephalus	Pineal region	Occipital craniotomy	Diplopia	GTR	Mixed: mature teratoma and germinoma	Chemo/XRT	5 yrs	No
20 yr	M	Headaches, ataxia, emesis, blurry vision	Pineal region	Suboccipital craniotomy	Parinaud syndrome, multiple shunt revisions	GTR	Mixed: teratoma and germinoma	Chemo/XRT	1 yr	No

Chemo = chemotherapy, CN = cranial nerve, DI = diabetes insipidus, F = female, GTC = generalized tonic-clonic, GTR = gross total resection, M = male, mo = months, NA = not available, SIADH = syndrome of inappropriate antidiuretic hormone secretion, STR = subtotal resection, XRT = radiation therapy, yr = years.

was not present. The absence of PLAP and membranous CD117 (C-kit) staining argued against a component of germinoma. Negative staining for hCG was against a component of choriocarcinoma. Therefore, the high-grade features of the tumor, in conjunction with the expression of pan-cytokeratin and CD30, supported a diagnosis of a component of embryonal carcinoma in this mixed malignant germ cell tumor.

2.3. Illustrative Patient 3

Our third patient was a 38-year-old man who presented with severe burning back and neck pain extending bilaterally to his deltoid muscles, as well as difficulty standing and walking. An MRI

from an outside institution revealed an intradural, intramedullary mass at the T2 level concerning for a cavernous malformation (Fig. 2E–G). He underwent a T1 to T3 laminectomy with exploration of this mass, which resembled a tumor, rather than a cavernous malformation. As a result, only a biopsy was performed, and the histopathology suggested a glial neoplasm consistent with an ependymoma. Because a subtotal resection had been performed and the pathologic diagnosis was inconclusive, a multilevel laminectomy with further resection of the tumor (due to adherence to the spinal cord) was performed. Histopathology demonstrated epithelial tissue, as well as rare adipocytic and mesenchymal elements, consistent with a teratoma. There was positive immunostaining for keratin and endothelial membrane antigen,

Table 2
Demographic and clinical characteristics of spinal teratoma patients

Age	Sex	Preoperative symptoms	Tumor location	Surgical approach	Postoperative symptoms	Extent of resection	Final pathology	Adjuvant treatment	Follow-up	Recurrence
27 yr	F	NA	Midthoracic spine, intradural/intramedullary	Multiple thoracic laminectomies	NA	STR	Teratoma	Repeat surgery	13 yr	Yes
43 yr	F	Right chest pain	T9 extradural	Right T9 costo-transversectomy	None	GTR	Mature teratoma	None	7 yr	No
38 yr	M	Back/neck pain, LE weakness	T2 intradural/intramedullary	T1–T3 laminectomy	Improvement in LE weakness	STR	Teratoma	None	4 yr	No
37 yr	M	LE weakness, bladder incontinence	T10–T11 intradural/intramedullary	T9–T12 laminectomy	Improvement in LE weakness	STR	Mature teratoma	Required subsequent spinal fusion for kyphoscoliosis	3 mo	No

F = female, GTR = gross total resection, LE = lower extremity, M = male, mo = months, NA = not available, STR = subtotal resection, yr = years.

consistent with an epithelial component in the tumor. The Ki-67 (MIB-1) stain showed only scattered positive cells, consistent with a low proliferation rate.

Postoperatively, the patient experienced significant improvement in his lower extremity weakness. He continued to improve clinically without any evidence of recurrent tumor on follow-up imaging at 4 years.

3. Results

The above three illustrative patients treated at our institution highlight unique aspects of the clinical features of intracranial and spinal teratomas. In this retrospective series, there were 15 patients with proven CNS teratomas; 11 in a cranial location and four in a spinal location (Table 1, 2). Among the patients with intracranial teratomas, nine were male and two were female. The average age was 15.8 years, ranging from 8.5 months to 52 years old.

The intracranial location of tumors in our cohort was typical, with the majority of teratomas found in midline areas, such as the pineal or sellar/suprasellar regions. More specifically, eight out of the 11 intracranial tumors were located in the pineal/third ventricular region (see Illustrative Patient 1, Fig. 1). There were patients with teratomas in highly atypical areas, such as the temporal lobe (see Illustrative Patient 2, Fig. 2) and frontal skull base (Table 1). The preoperative symptoms depended on tumor location, with the majority of patients presenting with symptoms of hydrocephalus (headaches, nausea, vomiting) which was not surprising for tumors arising from the pineal region. Ten patients underwent craniotomies (two bifrontal, five unilateral, four suboccipital), while one patient had a transsphenoidal resection.

Gross total resection was achieved in eight out of 11 patients. Most patients (n = 7) had tumors with mixed pathology: either mature or immature teratoma, although germinoma or another germ cell tumor type was also encountered (Fig. 3). All of the patients with mixed tumors underwent adjuvant chemotherapy

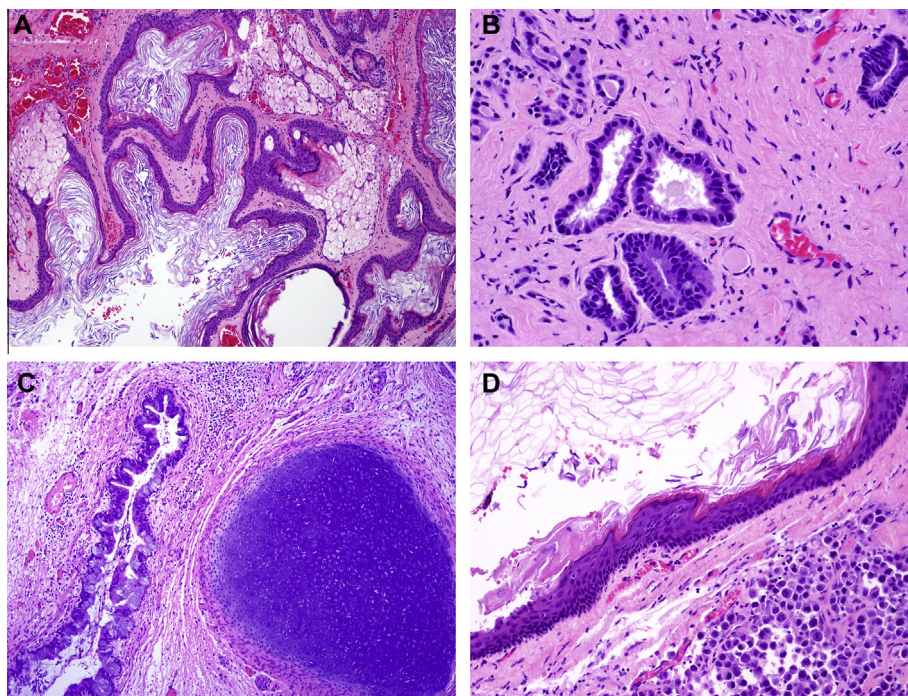


Fig. 3. Light microscopic images demonstrating tissues from all three embryologic germ layers, stained with hematoxylin and eosin. (A) Pineal region teratoma. Ectodermal component: mature squamous epithelium with orthokeratosis and adjacent sebaceous glands, resembling skin (original magnification $\times 100$). (B) Spinal teratoma (Illustrative Patient 3, Fig. 2E–G). Endodermal component: glandular structures (original magnification $\times 400$). (C) Pineal region teratoma. Endodermal and mesodermal components: intestinal-type glands with mucin filled goblet cells (left), with adjacent focus of mature hyaline cartilage (right) (original magnification $\times 100$). (D) Pineal region teratoma. Mature squamous epithelium (top left) with adjacent small focus of malignant transformation, germinoma (bottom right) in an otherwise mature teratoma (original magnification $\times 200$). (This figure is available in colour at <http://www.sciencedirect.com>.)

and radiation following their surgical resection. Amongst the patients with mixed tumors, a recurrence was noted in one patient who underwent subtotal resection due to the location of their initial tumor.

In four cases where the pathology demonstrated a pure teratoma, two patients did not receive adjuvant therapy after surgical resection. One patient with a malignant teratoma had a very poor neurologic examination and because of the presence of extensive disseminated disease, he was transitioned to comfort care and subsequently died (Illustrative Patient 2). Another patient with benign mature teratoma experienced “recurrence,” with the development of an astrocytoma at the same site as his prior pineal region teratoma, which was treated with radiation therapy (Illustrative Patient 1).

Among the patients with spinal teratomas, there was an equal incidence in males and females. The average age for spinal teratomas was 36.3 years old. All four spinal teratomas were located in the thoracic spine, three out of four were intramedullary, and all had benign histopathology (mature teratoma). Only one out of the four patients underwent a gross total resection, but in average follow-up of 5.9 years only one patient experienced recurrence, requiring repeat surgery.

4. Discussion

Because of their rarity, there is a limited number of reports describing CNS teratomas. The largest previous series include one with 14 cases of intracranial teratomas in children [1], another with 31 patients from South Korea [2], and a pathologic study of 64 cases of fetal intracranial teratomas [15]. The most recent study that we are aware of identified 12 pediatric intracranial teratomas, as well as 23 pediatric spinal teratomas treated at a center in India [19].

All these studies [1,2,19] suggest that intracranial teratomas are more common in males than females, which is consistent with our series where nine out of 11 patients were male. Other studies note the predilection for younger ages at diagnosis, which was also true in our series, where the mean age at diagnosis was 15.8 years (ranging from 8.5 months to 52 years old). Intracranial teratomas are usually located in midline locations such as the pineal region, suprasellar cistern, basal ganglia, and thalamus [2]. The presented case of an intracranial teratoma arising in the temporal lobe in a 52-year-old man (Illustrative Patient 2) is therefore atypical, not only in terms of location, but also for the age of presentation.

This series reveals that patients with intracranial teratomas can have a diverse clinical presentation, depending on the tumor location. The most common symptoms are headaches and emesis, although one infant with a frontal skull base teratoma extending into the posterior pharyngeal space presented with respiratory obstruction requiring tracheostomy. Another patient presented with bitemporal hemianopsia, irregular menses, and galactorrhea – symptoms usually associated with a pituitary tumor. All of the patients in this series were treated with surgical resection, and gross total resection was achieved in eight out of 11 patients. The high rate of gross total resection and low recurrence rate is consistent with the good prognosis for teratomas described in the literature, with 5-year survival rates ranging from 87 to 100% for benign mature teratomas [1,10,11] and from 33 to 71% for malignant teratomas [1,11].

Tumor recurrence occurred in four out of 11 patients with intracranial tumors. One patient had a malignant teratoma and another was mixed teratoma/germinoma. Our Illustrative Patient 1 describes an unusual situation of a “recurrence” after resection of a benign mature teratoma, where the patient developed an astrocytoma at the same site as his prior pineal region teratoma. This

is most likely *de novo* metachronous tumor development, rather than recurrence of the original mature teratoma. Nevertheless, this is a rare event, with very few case reports of either teratomas undergoing malignant transformations (to a yolk sac tumor [20] or medulloblastoma [21]) or metachronous tumors developing at the same site [22].

Like intracranial teratomas, spinal teratomas are exceedingly rare. The literature reports fewer than 170 total cases of spinal teratomas to our knowledge [23]. A recent review article summarizes some of the key features of spinal teratomas, including male preponderance and a predilection for the thoracic spine or conus medullaris [23]. In our series of spinal teratomas, there was an equal number of males and females, which likely is a consequence of the small sample size. The average age of patients with spinal teratomas in our series was higher than those with intracranial teratomas (36.3 versus 15.8 years old). This suggests that spinal teratomas may affect a different patient demographic than cranial teratomas, although our patient population is too small to draw any statistically significant conclusions. All patients with spinal teratomas had tumors located in the thoracic spine, a common location for spinal teratomas [23]. All of the spinal teratomas had pathologic features consistent with a mature teratoma. The recurrence rate was low (25%), consistent with what has been reported previously [24].

5. Conclusion

Our case series of 15 CNS teratomas highlights the diversity in presentation and treatment of these rare tumors. The preoperative symptoms and surgical approach depend specifically on tumor location. Surgical resection is the treatment of choice for mature teratomas, and gross total resection was achieved in the majority of our intracranial and spinal teratoma patients. As expected, there is a low recurrence rate in patients with mature teratoma.

Conflicts of Interest/Disclosures

The authors declare that they have no financial or other conflicts of interest in relation to this research and its publication.

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