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## Teratomas in central nervous system: A clinico-morphological study with review of literature

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## Abstract

**Background:** Cranio-spinal axis teratomas are rare. This subset is interesting because symptoms can be varied, depending on the location. Histopathology is diagnostic; most of the lesions are benign. Rarely, malignancy develops in any of the somatic components. **Aims:** To study the demographic, clinico-morphological and follow-up data of central nervous system (CNS) teratomas. **Materials and Methods:** Cases diagnosed as mature or immature teratomas in the CNS over a 20-year period were included in the study. Clinico-radiological, demographic and follow-up data of these cases were analyzed. **Results:** A total of 14 tumors were diagnosed as teratomas. Of these, 11 were mature cystic teratomas; and 1 case each, of teratoma with malignant transformation, terato-carcinoma and mixed germ cell tumor (immature teratoma with germinoma). Six of the 14 cases were intracranial and 8 were spinal. Presenting features varied according to the location. Radiologically, contrast enhancement with predominantly solid component was suggestive of malignancy or an aggressive tumor. Morphologically, a variety of tissue derivatives were seen in the cases. Excision was curative or provided symptomatic relief in most cases; terato-carcinoma and mixed germ cell tumor patients needed adjuvant radiotherapy. **Conclusion:** CNS teratomas are rare. Morphology and location decide outcome.

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## Full Text

## Introduction

Cranio-spinal axis teratomas are rare. [1] The existing literature is confined to individual case reports and

occasional case-series. Except for sacrococcygeal location, teratomas constitute less than 0.5% of intra-spinal tumors. [2],[3] By definition, they are tumors of multipotential cells derived from all 3 germ cell layers and recapitulate normal organogenesis. Teratomas are hypothesized to arise by misplacement of multipotential germ cell. Broadly, they are classified as mature, immature and malignant. Age range at presentation is wide (birth to 57 years). Intracranial teratocarcinoma is a still rarer entity and has a poor prognosis. [4] Radiology is helpful in ascertaining nature of the lesion but is not diagnostic. Histopathology is the gold standard for diagnosis. Although cranio-spinal axis is an uncommon location, yet there has been considerable interest in this subset due to clinical heterogeneity and challenges in treatment. In this study, we retrospectively reviewed 14 cases of cranial and spinal teratomas, along with review of the possible explanations for their origin in the central nervous system.

## Materials and Methods

All cases diagnosed as intracranial or spinal teratomas during the period January 1989 to April 2010 were retrospectively reviewed. Clinical, demographic, radiological and treatment details of the patients were retrieved from the medical records. Formalin-fixed paraffin-embedded tissue was available for all the cases. An average of 4-8 hematoxylin and eosin (H and E)-stained sections were reviewed for all cases. Special stains and immunohistochemistry were done wherever necessary. They were categorized as mature or immature teratomas; teratomas with malignant transformation; and teratocarcinomas.

## Results

Excluding metastatic and lymphoid malignancies, 8,050 primary CNS tumor specimens were received in the Department of Pathology during the study period. Of these, 1,300 were spinal in location. There were 20 germ cell tumors, accounting for 0.2% of all tumors. Of these, 14 patients (6 female and 8 male) had teratomas and 6 had germinomas. Six teratomas were intracranial and eight were spinal in location. At their respective sites, teratomas constituted less than 0.1% of intracranial and 0.6% of spinal tumors.

The age range was 16 days to 45 years (mean, 15.9 years). One patient (Case 1) had congenital teratoma located in the cervical spine. Four of the 6 intracranial teratomas were located in the pineal region; and 1 each, in the suprasellar and parenchymal (left occipital lobe) location. Common presenting features were raised intracranial tension and visual disturbances in 4 of the 6 cases; and excessive urination and thirst, in 1 of the 6 cases. Spinal teratomas were equally distributed in the cervical (4/8, 50%) and lumbar regions (4/8, 50%). Patients with spinal teratomas presented with swelling (2/8), pain (3/8), bladder and bowel disturbances (2/8) and delayed neck-holding (1/8). Three patients had associated spinal deformity, like spina bifida and posterior arch deficiency. There were paresthesias in 4 of the 8 patients; and focal neurological deficits, in 2 of the 8 patients. ([Table 1]- Cases 1-8 are spinal and cases 9-14 are intracranial). Notable male predominance was seen in tumors of the pineal region. {Table 1}

### Radiological features

On magnetic resonance (MR) imaging, all lesions (except cases 7, 12 and 14) were solid cystic or predominantly cystic with a mural nodule without significant contrast enhancement or with minimal ring enhancement ([Figure 1] and b). These were lobulated, heterogenous, mixed-density masses, with few of them showing fat densities and specks of calcification. Mature teratomas were hypointense on T1-weighted images and hyperintense on T2-weighted images. In 2 cases (Cases 12 and 14), the tumors were predominantly solid without any cystic component and showed brilliant contrast enhancement. Both were located in the pineal region and histologically corresponded to teratocarcinoma and immature teratomas with germinoma, respectively. One tumor (case 7) was a solid cystic mass of heterogenous composition with brilliant contrast enhancement. Unlike others, these three lesions were uniformly hyperintense on T1- and T2-weighted images. The spinal teratomas were intradural and extramedullary, with only 2 of them (Cases 2 and 6) showing intramedullary component [Table 1]. {Figure 1}

## Surgery

Surgical details are shown in [Table 1]. Surgical approach was decided based on location of the tumor. Complete excision was defined as removal of >90% of the tumor. Anything less than that was labeled as incomplete excision. Two of the 4 tumors in a pineal location and 1 in a suprasellar location could not be excised completely. One pineal teratoma was small and circumscribed and so was easily excised. Debulking surgeries were done for cases where complete surgical resection was not possible. Adjuvant radiotherapy was given in Cases 7, 12 and 14 after the initial surgery. Surveillance imaging was done at 3 and 6 months post-surgery.

## Histopathological examination

All cases showed derivatives of 3 germ layers. The tissue types included epithelial tissues as squamous, respiratory and intestinal epithelia. Sebaceous and sweat glands were seen in a few cases. Cartilage with or without calcification, mature adipose tissue, fibrous tissue, mature smooth muscle, osteoid and glial tissue were seen in variable proportion [Figure 2]. Few cases showed colloid-filled follicles and pancreatic tissue [Figure 3]. {Figure 2}{Figure 3}

Case 7 had areas resembling other mature teratomas. In addition, there were cystic spaces lined by atypical squamous epithelium with loss of polarity, nuclear hyperchromasia with varying degree of chromatin density and focal intracellular keratin. Islands of neoplastic squamous epithelium were infiltrating the adjacent solid areas. Ki-67 labeling index was 88% in these neoplastic islands [Figure 4].{Figure 4}

Case 12 had areas resembling other mature teratomas, along with foci of nests of undifferentiated hyperchromatic cells. These cells had pleomorphic overlapping nuclei, scant cytoplasm and increased mitotic activity, lying against desmoplastic stroma [[Figure 5]a and b]. This was diagnosed as teratocarcinoma (teratoma with embryonal carcinoma).{Figure 5}

Case 14 had tissues representative of all 3 germ layers. In addition, there were foci of neuro-ectodermal tissue and immature cartilage. Extensive sampling done to assess the percentage of immature component revealed nearly 50% of the same. There were sheets of polygonal cells with prominent nucleoli [[Figure 5]c and e]. This was classified as mixed germ cell tumor (immature teratoma with germinoma).

To summarize, the results of morphology in correlation with age of patients were as follows: Immature teratoma (Case 14) and teratocarcinoma (Case 12) were seen in young adult males in this study. Malignant transformation (Case 7) was seen at 35 years of age. Seven of the 11 mature teratomas were seen in patients <15 years of age. Remaining 4 patients were adults or young adults.

Follow-up duration was variable, between 2 months (Case 13) and 7 years (Case 3). The data (wherever available) are shown in [Table 1].

There were no immediate postoperative complications. Long-term complications (recurrence, no improvement in vision) have been listed in [Table 1].

## Discussion

Teratomas of the brain and spinal cord are very rare. Tapper and Lack published a series of 254 teratomas in patients aged 21 years or less over a period of 54 years. [5] The tumor was located in the central nervous system in 9 (3.5%) patients, and only 4 (1.5%) tumors were located in the spinal canal, excluding those localized in the sacrococcygeal region, which constituted 40% of the total teratomas. They represented 0.5% of all intracranial tumors [6] and 2% to 4% of intracranial tumors in children. [6],[7] In the present study, there were 14 CNS teratomas, over a 20-year period, accounting for less than 0.1% in the brain and 0.6% in the spine. However, the proportion is higher if pediatric tumors alone are considered.

In a study of 18 intraspinal teratomas, [8] conus medullaris was the most frequent location (70.6%). Overall, males were more commonly affected than females (3:1). Adults were more commonly affected than children. Seven (41.1%) of the 11 patients had congenital dysraphic manifestations. In this study also, males were more commonly affected (8/14). However, congenital teratoma (Case 1) in the present study was seen in a female child. These findings are in accordance with those found in literature. [9] Cervical spine was as common a location as lumbar spine (4/8, 50%). Association with spinal defects was seen in 3 (37.5%) of the 8 cases; all of these were of children, and the results are similar to those of another Indian study of spinal teratomas. [10]

Within the brain, teratomas arise in the midline from optic chiasm to the pineal gland. [11] Midline is a location with great potential for misplacement of embryonal tissues. Intracranial teratomas may arise from pineal gland, quadrigeminal plate, wall of the third ventricle, suprasellar region or cerebellar vermis. [12],[13] Four (66.6%) of the 6 intracranial teratomas in our study were identified in the pineal region. Teratomas in the pineal region had a striking male predilection.

Two theories could explain the pathogenesis of germ cell tumors in the CNS. The germ cell theory hypothesizes that these tumors arise from primordial germ cells which have migrated aberrantly during embryogenesis and later undergo malignant transformation. In contrast, the embryonic theory suggests that these tumors arise from a mis-migrational pluripotent germ cell. [14] It is also proposed that while germinomas arise from germ cells, other non-germinomatous germ cell tumors, including teratomas, occur due to misfolding or misplacement of embryonic cells into the lateral mesoderm, causing their entrapment in various parts of the CNS. Movement of the primordial germ cells to the germinal ridges in developing embryo is probably under control of complex molecular events. [15],[16],[17] Important amongst these are extracellular matrix and chemotropic factors. In vitro studies have shown a role of growth factor  $\beta$  to initiate migration of primordial germ cells. The fetal hypothalamus matures at the same time as that of migration of primordial germ cells. One possible explanation is that hypothalamus may secrete chemotropic factors to cause germ cell mis-migration to diencephalon. Further, congenital or acquired aberrant molecular events may cause micro-environmental changes, leading to CNS germ cell tumors.

On MRI, the lesions are hypointense on T1-weighted and hyperintense on T2-weighted images. They are non-enhancing on contrast. MRI definitely helps to ascertain the location and extension of the tumor but is not definite for diagnosis. Intramedullary component has been shown to be associated with meningocele or split-cord malformation in earlier studies [10] ; however, no such association was seen in our patients (Cases 2 and 6). Malignant nature, as in immature teratoma, teratocarcinoma; or malignant transformation, as in longstanding teratomas, is suspected if the lesion is predominantly solid and/or contrast enhancing, as was seen in Cases 7, 12 and 14 in our study. A thorough sampling is thus mandatory.

Histopathology is the definitive diagnostic tool. Mature teratomas exhibit variable proportion of components derived from all 3 germ layers, i.e., ectoderm, endoderm and mesoderm. Stratified squamous, respiratory and gastrointestinal epithelia along with pilosebaceous units, cartilage teeth and bone are seen. Glial tissue is not uncommon. Malignant transformation may occur in any of the somatic components of mature cystic teratomas. These have a very poor prognosis. Squamous cell carcinoma is the most common type. A variety of non-epithelial malignancies, including sarcoma, primitive neuro-ectodermal tumor and leukemia, may occur. [18],[19],[20] Malignant transformation (squamous cell carcinoma) was identified in 1 of our patients; however, sarcomatous change was not seen. In 1 of the cases (Case 12), mature teratoma was one of the components of mixed germ cell tumor in association with embryonal carcinoma. Intracranial teratocarcinomas are rare malignancies and have been reported in literature with extracranial metastasis. [4]

Treatment is aimed at radical resection of tumors wherever possible. In the spine, the type of surgery chosen depends on the age of the patient. [6] In children, extensive laminectomies may lead to spinal instability. This is because in children, spinal stability is dependent on dorsal ligaments; whereas in adults, it is provided mainly by facet joints. So laminotomy and laminoplasty should be done in children. In contrast, laminectomy is usually preferred for adults. [21],[22] Completeness of excision depends on the site of excision. Similar treatment protocols were followed in our patients. Prognosis is poor for teratocarcinomas and teratomas with malignant transformation. In case of the former, surgery has to be supplemented by chemotherapy and/ or radiotherapy because of propensity to metastasize. [4] Intracranial location of the lesion decides the surgical approach that

must be used in brain.

In conclusion teratomas are rare in the central nervous system. Pineal region is the commonest site in brain. Cervical spine is as common a location for spinal teratomas as is the lumbar location. Diligent search for immature or malignant component is required as these patients need adjuvant therapy along with surgery.

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