Intradural spinal teratoma: evidence for a dysembryogenic origin

Report of four cases

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Intradural spinal teratoma is a rare tumor that can be associated with dysraphic defects. Although the origin of these tumors is traditionally thought to be secondary to primordial germ cells misplaced early in embryogenesis, the pathogenesis of intraspinal teratoma remains unclear. The authors present a series of patients in whom an intradural teratoma arose at the same site as a developmental spinal cord abnormality, including a split cord malformation, myelomeningocele, and lipomyelomeningocele. It is postulated that these lesions were the result of a dysembryogenic mechanism and were not neoplastic.

KEY WORDS • myelomeningocele • intraspinal teratoma • spinal dysraphism • embryogenesis • split cord malformation

Virchow\(^{81}\) may have been the first to describe an intraspinal teratoma. Although a clear description of its “tridermal” elements was not given, the intraspinal tumor contained connective tissue, fat, and cartilage. The literature contains inconsistencies regarding the classification of intraspinal teratomas. The difficulty results in part from the rarity of teratomas located within the spinal canal, as well as the various terms that have been applied to similar entities by different authors.\(^{1,10,11,19,34,42,44,47,48,53,56,62–64,67,71,74,80,84,85}\) The definition of teratoma has ranged from a tumor derived from only two primitive germinal layers to the concept that it represents an “undeveloped twin,” as suggested by Bucy and Haymond.\(^{11}\) The current and most adequate classification states that a teratoma is a mass composed of derivatives from all three primitive germ layers and it distinguishes between mature and immature forms based on the degree of differentiation.\(^{72}\)

The origin of masses composed of elements of various primitive germ layers has been the subject of much speculation, and several theories have been offered in attempts at explanation.\(^{6,8,9,24,25,31,43,66}\) The traditional view is that intraspinal teratomas arise from primordial germ cells misplaced from the primitive yolk sac. However, a dysembryogenic origin of intraspinal teratoma is suggested by the following observations. First, review of the literature indicates that there may be an association between dysraphic processes and teratomas.\(^{3,6,11,14,26,35,38,44,45,50,65,69,79}\) Second, recent embryological investigations have demonstrated the pluripotential nature of the developing caudal spinal cord, which can potentially form all three germ layers.\(^{30,31,78}\) Moreover, most central nervous system teratomas occur in midline structures and could be derived from pluripotential cell rests at sites of early neural tube closure.\(^{49,72}\) Third, a dysembryogenic or prenatal origin has recently been proposed for other neoplasms that typically occur in the midline. A likely origin of medulloblastoma, for example, is the pluripotential external granular cell layer of the cerebellum.\(^{13}\) These data indicate that a dysembryogenic process may give rise to intraspinal teratomas that traditionally have been thought of as neoplasms.

We treated four patients who underwent exploration or repair of a congenital spinal cord abnormality. At each
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operation an abnormal tissue mass was discovered. This mass was found to have elements of all three dermal layers, which is consistent with a diagnosis of teratoma. This rare constellation of findings, namely mature (tridermal) teratoma associated with a myelomeningocele, lipomyelomeningocele, or split cord malformation, strongly indicates a myelodysplastic origin of these teratomas. We suggest that these tumors and perhaps others are a product of abnormal development of the pluripotential embryonic spinal cord mesenchyme, especially the caudal cell mass.

Case Reports

Case 1

History. This 31-year-old woman had a large (9–10 cm) lumbar myelomeningocele at birth, and she underwent surgery for delayed closure at 6 months of age after a cerebrospinal fluid leak and a bout of meningitis. At the time of closure, the patient had a marked sensorimotor deficit in the right lower extremity with fairly good movement in the left lower extremity. Intraoperative findings (G Odom, personal communication, 1997) included identification of a large abnormal bone spicule on the left side that extended back into the sac a distance of 1.5 cm. No fluid collections were identified. The dura was closed using a free fascial graft, and the skin defect was repaired with a full-thickness graft rotated from the region of the right buttock. Pathological examination revealed fibrous connective tissue and neural elements consistent with a diagnosis of myelomeningocele (Fig. 1). The patient later underwent placement of a ventriculoatrial shunt. Since that time she had undergone multiple orthopedic procedures and two shunt revisions. Her paraparesis had slowly worsened and 1 year prior to presentation she developed progressive radicular pain in the T10–L1 distributions associated with back pain.

Examination. At presentation her neurological examination revealed 4/5 iliopsoas strength bilaterally, 1/5 left quadriceps strength, and 0/5 in all other groups. Her lower extremities were areflexic and sensory examination showed intact sensation through L-2 bilaterally. Bladder and bowel function were unchanged; she maintained a regimen of self-catheterization and laxatives.

Radiographic Studies. Total spine magnetic resonance (MR) imaging revealed evidence of a large intradural cystic mass in the lower spinal canal that had signal characteristics suggestive of both solid and cystic components. This mass tethered the spinal cord. In addition, a small syrinx at the T9–10 level and butterfly vertebrae were revealed (Fig. 2).

Operation. The patient underwent surgery for release of the tethered spinal cord and resection of the cyst. Intraoperative electromyographic responses were monitored throughout the procedure from the T-10 down through the L-3 level. At exploration the arachnoid was found to be densely calcified and adherent to several dorsal nerve roots. The spinal cord was followed inferiorly and appeared to flare open at the L3–4 level. A large cyst was encountered here and 30 ml of thick brownish fluid was removed. The walls of the cyst appeared to be glistening membrane, much like ependyma. Biopsy specimens of the wall and an adjacent reddish-tan mass were obtained for pathological examination. After identification of several dorsal nerve root remnants, the cyst was partially resected, allowing the cord to fall freely into the ventral portion of the thecal sac. Following these maneuvers, recordings from the right L1–3 root levels showed significant improvements of 98% and 53% in latency and amplitude, respectively. Improvements in latency and amplitude of 60% and 46% were noted on the left side. The remainder of the cystic mass was then resected, as was a bone spur that separated two hemicords.

Pathological Examination. The mass resected from the caudal spinal cord consisted of a lobular portion of cartilage centrally surrounded by a thin superficial layer of respiratory mucosa. This entire structure was found within a dilated cyst that was lined internally with cuboidal ependymal cells supported on a thin membrane of woven astrocytic cells. No other epithelial or mesenchymal components were identified in this tissue (Fig. 3).
Postoperative Course. There were no complications postoperatively and the patient noted an immediate and dramatic improvement in her flank and back pain. Results of her neurological examination were unchanged and pain relief remained stable at a follow-up interval of 1 year. An MR study obtained postoperatively demonstrated an untethered spinal cord and gross-total resection of the cystic mass (Fig. 4).

Case 2

History. This 1-day-old boy born after a 39-week gestation was noted to have an asymmetric lumbosacral myelomeningocele. He had no other congenital anomalies other than colpocephaly revealed on ultrasonographic studies. Lower limb strength was excellent down to the level of the ankles.

Fig. 2. Case 1. Preoperative T1-weighted MR images. Upper: Sagittal image in which a large heterogeneous intraspinal mass extending from the L3–4 disc space to the sacrum can be identified, demonstrating signal characteristics compatible with both solid and cystic components. Lower: Axial image revealing the mass filling the lower spinal canal and a cleft in the vertebral body.

Fig. 3. Case 1. Photomicrographs of tissue obtained intraoperatively and stained with H & E. Upper: Section of the solid mass resected from the filum terminale, revealing a central mass of benign, slightly disorganized cartilage surrounded by respiratory mucosa complete with bronchial glands, smooth muscle, lymphocytes, and ciliated columnar epithelium. The cystic portion was lined with cuboidal ependymal cells supported on a thin membrane of woven astrocytic cells. Original magnification × 100. Lower: The ciliated ependymal cell–lined cyst rests on connective tissue in which a neuroglial rest is found. Original magnification × 150.
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Operation. The patient underwent immediate surgery for closure of the myelomeningocele. At exploration a split cord malformation was discovered with dysplastic-appearing tissue extending from the dorsal aspect of the left hemicord. This tissue was resected, as was a cartilaginous diastem. The ventral dura was opened and reflected off the diastem. No ventral communications were present.

Pathological Examination. The resected dysplastic tissue contained cutaneous epithelium with inflammatory changes in addition to scattered neuroglial rests in the dermis. Multiple foci of mature enteric epithelium were found surrounded by muscle, fat, and neural tissue, findings consistent with a diagnosis of mature teratoma (Fig. 5).

Case 3

History. This 5-year-old boy had previously undergone resection and closure of a lipomyelomeningocele and subsequently did well. He presented 4 years later with symptoms of increased stumbling and progressive bladder dysfunction. Repeated MR imaging demonstrated an increase in the size of the residual mass and tethering of the conus.

Operation. The patient underwent surgery for resection of the residual mass and untethering of the spinal cord. A yellowish-tan mass was identified and resected down to the dorsal aspect of the caudal spinal cord.

Pathological Examination. The specimen was a complex lesion composed of fibrous connective tissue in which were found lobules of mature fat. Nodules of benign-appearing cartilage and rests of neural tissue exhibiting collections of ependymal cells and irregular blood vessels were scattered throughout the mass.

Case 4

History. This 14-month-old boy underwent a chest x-ray for a respiratory infection and was noted to have hemivertebrae at T-5 and T-6 and an absent sixth rib. On MR imaging a split cord malformation and a cystic mass that was confluent with the left hemicord were revealed. A diffuse syrinx was present and extended from the cervical spinal cord into both hemicords and into the cystic mass via the left hemicord. Additionally, the spinal cord was tethered. Neurologically the patient was able to walk at age 12 months, sensation was decreased in the left lower limb, and reflexes were normal.

Operation. The patient underwent surgery for exploration of the mass and release of the tethered spinal cord. At surgery the dura was opened, revealing two hemicords from the T4–7 level with no median septum. The cystic mass was seen to merge with the caudal hemicord and extend toward the neural foramen at this level. No ventral communications were present and the cyst was entirely intradural. The mass contained clear viscous fluid and one portion of the wall was 1 to 2 cm thick. It was dissected away from the spinal cord and resected, and the tethered cord was also released.

Pathological Examination. The specimen consisted of dense fibromuscular tissue that contained ganglion cells and portions of nerve. Eosinophilic fibrillar tissue consistent with a neural origin was scattered throughout the sample, and a single lymph node was present. Also present were portions of muscle and bone embedded in fibrofatty tissue, and tall columnar epithelium lined one margin of the mass.

Discussion
Definitions of Terms

Many terms have been applied to intraspinal cystic masses that contain elements derived from two or three of the primitive germ layers. Terms such as teratoid, teratoid cyst, teratoma, cystic teratoma, teratomatous cyst, and neurenteric cyst have been used interchangeably. Willis defined a teratoma as “a true tumor or neoplasm composed of multiple tissues of a kind foreign to the part in which it arises.” Russell and Rubinstein later described teratomas as tumors that contain ectodermal, mesodermal, and endodermal elements. Two types exist: 1) mature teratomas composed of well-differentiated elements; and 2) immature teratomas that contain primitive elements derived from any or all of the three germinal layers. Teratomas may have a cystic component. Wilkins and Rossitch recently classified intraspinal cystic teratomas as a subset of neurenteric cysts, whereas ter-
atoid and teratomatous cysts were subclassified separately. The term “teratoid” has been used to describe tumors containing either poorly differentiated structures or elements derived from only two germinal layers. However, teratoid should probably be used only to refer to masses containing mature derivatives of two germinal layers. The use of the term “teratomatous cyst” has been debated recently in the literature.

Other cystic intraspinal lesions such as epidermoid and dermoid cysts have not been confused with teratomas. However, an intraspinal neuroenteric cyst may contain histological elements similar to those found in teratomas. Intraspinal neuroenteric cysts contain at least one element from the gastrointestinal tract or the tracheobronchial tree and may have a complex morphological composition. Thought to be developmental in origin, these cysts typically are associated with ventral spinal defects and may contain epithelial invaginations. Enterogenous cysts, gastrocytomas, intestinomas, and foregut cysts are thought to be similar in origin to neuroenteric cysts and are usually classified as subsets of the latter. As Wilkins and Rossitch point out, classification systems are often not adequate to describe all intraspinal cysts because there exists an increasingly complex histological spectrum with epidermoid cyst at one end and tridermal teratoma at the other.

**Tumor Pathogenesis**

*Traditional View.* The traditional view is that early in embryogenesis primordial germ cells from the yolk sac become misplaced, most commonly into midline structures, after which they can give rise to germ cell tumors, including teratomas. The presence of Barr bodies (intranuclear inclusions of the XX type) in teratomas in male patients has been looked on as evidence that these tumors are of germ cell origin. However, it has been pointed out that it may not be valid to assume karyotype from nuclear sex chromatin, because the latter can represent XO or mosaic forms of nuclear material. Therefore, one piece of evidence in support of the germ cell origin of teratomas may be called into question. Moreover, the germ cell theory does not fully explain the usual midline location of teratomas in areas such as the mediastinum and diencephalon. It may be more reasonable to postulate local mechanisms that went awry to explain these midline anomalies. Jennings, et al. have suggested that local factors play a major role in the development of diencephalic “germ cell” tumors, including teratomas. Gonadotropin secretion from hypothalamic nuclei may either draw germ cells to this area or alter normal development patterns. Jennings, et al., offer several observations as supporting evidence that hypothalamic gonadotropins have a local inductive role in the development of germinal tumors.

*Other Theories.* Several other theories have been presented in the literature concerning the development of
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intraspinal teratoma or teratoma-like masses. Among these are the contributions of the “split notochord syndrome” by Bentley and Smith, and Bremer’s hypothesis of the “accessory neurenteric canal.” Although these theories largely represent attempts to explain the dysembryogenic origin of neurenteric cysts, these cysts may share many histopathological characteristics with intraspin al cistic teratomas. Therefore, a dysembryogenic mechanism could also lead to formation of tissues found in a teratoma. The “entodermal-ectodermal adhesion syndrome,” proposed by Prop, et al., would result in a spinal mass containing elements of different dermal layers. All of the preceding theories imply that abnormal embryogenesis could be the cause of masses composed of multiple germ layers.

**Disembryogenic View.** The caudal cell mass of the developing embryo is an aggregate of undifferentiated mesenchymal cells that represents the remnants of the primitive streak and Hensen’s node. The pluripotential nature of this caudal cell mass mesenchyme has been demonstrated by in vitro culture and in vivo grafting to form cell types found in all three germ layers. The differentiation of this caudal cell mass into tissue types that are derived from the three germinal layers elsewhere in the body has been shown in chick and mouse embryos. The direction of differentiation is known to be guided by inducer substances and regulatory genes in animal models, and similar mechanisms are thought to function in humans.

Askanazy first introduced the developmental concept that teratomas may arise from abnormal tissue primordia early in embryogenesis. This concept relies on the understanding that development requires a complex interaction among the intrinsic cellular genetic blueprint, inductive cell-cell interactions, and the influence of environmental factors. Any aberration of the developmental scheme, therefore, could result in abnormal neural development in general and in the formation of a teratoma in particular. The theory of a “primary organizer” that influences embryogenesis was discussed by Budde. He and others suggested that teratomas were the result of maldevelopment of the primitive streak, which would also account for the median sites of extragonadal teratomas. The association of spinal cord development and the formation of teratomas was emphasized by Pickens, et al., in their report on an infant who at necropsy was found to have a spinal cord almost entirely replaced by a true teratoma. Others also report the association between intraspinal teratomas and various myelodysplastic defects.

**Role of Early Regulatory Genes.** During the past 10 years, a variety of developmentally regulated genes have been implicated in pattern formation of the embryo in general and of the nervous system in particular. Many classes of regulatory factors are thought to be important for embryonic development. They include growth factor genes, differentiation-inducing genes, diffusible morphogens, oncogenes, and genes that code for transcription factors. The genes that code for transcription factors are the most interesting.

Systematic genome dissection of *Drosophila melanogaster* has revealed many key genetic loci important in the control of the organization of the embryonic body plan. Molecular analyses have shown that a 180-bp coding region, the homeobox, was contained in many of these regulatory genes. Cross-hybridization experiments in which the *D. melanogaster* homebox was used as a probe revealed that many species, including mice, chicks, and humans, have homebox genes. Genes that contain a homebox will code for DNA binding proteins that regulate the transcription of other genes. The conservation of this DNA sequence across species lines, its ability to bind DNA, and its spatiotemporal expression patterns, especially in the developing nervous system, underscore the importance of the homebox in embryonic development.

Several homebox-containing genes are expressed in the caudal cell mass of experimental embryos and appear to be important for cellular differentiation. In fact, several candidate genes such as Pax-3 and Brachyury (T locus) have been found to have mutant forms that induce neural tube defects in animal models and perhaps in humans.

**Inductive Interactions.** In addition to regulated genes, which govern regional embryological development, the complex patterning and cellular identity in the embryo likely involve cellular interactions. The process in which one group of cells controls the fate of neighboring cells is known as embryonic induction. Inductive interactions involve two components: 1) an inducing cell that signals and 2) a responding cell that directly or indirectly controls gene expression. The signal from the inducing cell can anchor to the responding cell’s membrane, bind to extracellular matrix components, or be secreted freely as a diffusible molecule. The responding cell must be competent to recognize the signal, transduce the signal across the intracellular environment, and activate transcription. For example, the inductive events that occur during the formation of the chick embryonic axis have been well studied and the inducing tissues and local signals have been identified. In chick embryos a structure known as Hensen’s node induces the proper axis and is defined by expression of several genes. Its ability to induce a new ectopic axis when transplanted demonstrates the significant effects of inductive interactions. The combination of regulatory genes, inductive interactions, and the pluripotential embryonic caudal spinal cord provide the milieu in which normal tissues may de-velop.

The dysembryogenic view, therefore, proposes that mutated genes important for normal early neural development and cellular differentiation and/or absent or deficient inductive signals led to the constellation of findings in our patients. Although the caudal cell mass is probably the most studied part of the embryonic spinal cord, it is possible that other segments may give rise to abnormal tissues under the proper circumstances. Our theory furthers the suggestion by other authors that perhaps multiple dysembryogenic mechanisms are involved in the pathogenesis of intraspinal teratomas and possibly other “tumors.”

**Conclusions.**

By a strict morphological definition, the masses found in our patients were mature teratomas because well-differentiated derivatives of all three germinal layers were pre-
ent. In Case 1, we postulate that the teratoma as well as the split cord malformation were initially present at the time of myelomeningocoele closure. The fact that these findings were not recognized at that time was due to limited surgical exploration and the lack of adequate imaging techniques.

The presence of an intradural teratoma in association with a split cord malformation, myelomeningocoele, or lipomyelomeningocoele is a rare constellation of findings. The multiple concurrent and contiguous abnormalities in our patients suggest that a single local process, instead of multiple processes, led to their formation. As noted previously, the caudal cell mass in other species can give rise to tissue normally derived from the three primitive dermal layers. We propose that in humans this pluripotent embryonic caudal mesenchyme can give rise to teratomas and other congenital "tumors" due to the dysfunction of several factors that probably involve gene function and cellular inductive interactions. Moreover, the findings in Case 4 indicate that a similar process may occur in other segments of the developing spinal cord. The fact that each teratoma arose in an area of known aberrant embryological development also indicates that the origin of each "tumor" is a part of the same dysembryogenic process.

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