Diversity Among Teratomas, with a Historical Perspective

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The complex and diverse nature of teratomas causes confusion on several levels – diagnostically, pathogenetically and biologically. It is the intent of this talk to help clarify some of the confusing aspects of teratomas and to discuss their diagnostic pitfalls. Both pediatric and adult teratomas will be discussed, including those occurring in the gonads and at extragonadal sites (sacroccocygeal and mediastinal). It will become apparent that patient age, gender and site of origin are all critical factors that greatly impact on the biology of human teratomas. These differences can be understood when viewed in a pathogenetic context, which necessarily entails a consideration of the pathogenesis of germ cell tumors in general. It will also become apparent that a major reason for the confusion regarding human teratomas can be related to outmoded historical concepts that, to some extent, continue to persist despite ample evidence against them. The sources of these concepts will be touched upon and acknowledgement given to those who were key in resolving long-standing misconceptions.

The term “teratoma” derives from the Greek word “τέρατα,” which literally translates as “monsters.” A “teratoma” therefore is a “monster tumor” or “monster growth,” and it is apparent that the same root gives rise to “teratogenic,” which therefore translates to “monster forming.” In all probability “teratoma” was first applied to the circumstance of a malformed, monozygotic twin that was fused to an external body site of its genetically identical sib. This condition, today, is frequently termed “fetus in fetu.” Thus, the original “teratoma” referred to a congenital malformation, but it probably was relatively quickly adapted to what we would now regard as a true neoplasm rather than a malformation, namely the sacrococcygeal teratoma of infancy, because it, too, commonly appears as a “monstrous” protrusion from an external body site, although it is rarely fetiform.

It is speculative to determine how “teratoma” became used for the common gonadal tumors, but it appears probable that it came about as the microscope came into use in pathology. It should be recalled that until the middle of the 19th century pathology was almost exclusively a “gross only” discipline. However, as the microscope became more widely available and tissue sectioning and staining were refined, various lesions, mostly
from autopsies, were more and more subjected to microscopic examination. In this way similarities between sacrococcygeal and gonadal teratomas could be recognized and both lesions classified into the same group of neoplasms.

It is interesting to note that renowned pathologists, although recognizing that the sacrococcygeal and gonadal neoplasms were both “teratomas,” continued to draw a distinction between them based on their site of origin. In 1956, Dr. Pierre Masson, in his text, *Human Tumors*, drew a distinction between the “external” teratomas and the “internal” (or gonadal) ones. The “external” teratomas referred mostly to the sacrococcygeal and epignathic teratomas seen in children, and Masson felt they were explainable based on anomalies of the “organizers of Spemann.” This refers to the concept, originally put forth by the Nobel prize-winning embryologist, Hans Spemann, that the structures formed by embryonic cells are determined by diffusible substances from the local microenvironment. Today we would regard these “organizers” as signaling molecules that stimulate stem cells to develop along certain pathways. Thus, in Masson’s opinion, the “external” teratomas are not derived from germ cells but are, in a sense, malformations caused either by aberrations in signaling pathways or by inappropriate persistence of cellular pluripotency in a tissue niche with active cell signaling. On the other hand Masson fully endorsed that the gonadal teratomas were derived from germ cells, and he attributed them to parthenogenesis. As it turns out, this is about half correct; it is almost entirely true for ovarian teratomas where a parthenogenetic origin has been nicely demonstrated by molecular techniques (see below), but it is untrue for most testicular teratomas.

In my opinion, there is a great deal of merit to Masson’s belief that the extragonadal teratomas do not derive from germ cells but from embryonic cells. Firstly, these tumors disproportionately occur in infancy, when embryonic errors would be most manifest. Additionally, if the alternative explanation is misplaced germ cells (as is commonly cited), how many of us can say we have ever identified such a cell in an extragonadal location? It is also well established that the germ cells, when separated from their supporting gonadal cells (Sertoli and granulosa), undergo rapid apoptosis. I have also seen a case where cells resembling primordial germ cells selectively populated nests of thymic epithelium but were not in the associated stroma. It is difficult to believe that these cells migrated from the embryonic yolk sac and restrictively populated this component of the thymus; what appears more plausible is that cells within the thymic epithelium underwent reversion to a primordial germ
cell phenotype, a feat analogous to what stem cell biologists are accomplishing in the laboratory with the production of induced embryonic stem cells.

It’s instructive to see what the prevalent concepts regarding teratomas (and germ cell tumors more generally) were in the early part of the 20th century. Many concepts that were formulated then continued for decades thereafter. A good source is the classic textbook by Dr. James Ewing, *Neoplastic Diseases: A Text-Book of Tumors*, which was published in 1919 and was really the first credible pathology text authored by an American. Ewing was a great student of the literature and his views really represent a synthesis of the medical writings of his time. He recognized that both ovarian and testicular “teratomas” were of germ cell origin and divided them into 3 groups: 1) adult teratomas or embryo-omas (resembling adult or fetal tissues); 2) embryoid, teratoid or mixed tumors, which are “adult teratomas” with a component of “an embryonal malignant tumor” (the latter being one of the primitive germ cell tumors or a somatic-type malignancy) and 3) an embryonal malignant tumor (what we would consider today to be seminoma, embryonal carcinoma, PNET, etc.). This viewpoint is later seen in what became known as the British Testicular Tumour Panel classification, where almost all of the germ cell tumors were considered variants of teratoma (e.g. – embryonal carcinoma is “malignant teratoma, undifferentiated”). The fundamental concept is that teratoma develops initially and the primitive components represent “dedifferentiation” or “malignant degeneration” of teratoma. As it turns out, this sequence is opposite what usually happens in the testis (as will be discussed) but is accurate for the most common form of malignancy in ovarian teratomas (squamous cell carcinoma developing in a long-standing mature cystic teratoma). In this model there is no need to distinguish teratomas by site of origin since their biologic behavior is entirely predictable based on their appearance – i.e., whether or not an embryonal malignant tumor is present. The difference in behavior of testicular and ovarian teratomas was therefore explained on the basis of the much greater tendency of testicular teratomas to have such a component. Unfortunately, this misconception is carried forth well into the middle of the 20th century, where it is again reiterated in the AFIP fascicle authored by Dr. Rupert Willis in 1951.

A landmark in testicular tumor pathology and our understanding of testicular teratomas occurred in 1946, when Drs. Nathan Friedman and Robert Moore published their paper, “Tumors of the Testis: A Report on 922 Cases” (Military Surgeon 1946:99:573-593). Unfortunately, the evidence they presented appears to have been largely ignored for the ensuing 20 years. Among the seminal observation made by Friedman and Moore was that
on follow-up 13% of patients with pure teratomas of the testis were living with metastases and an additional 15% had died of tumor. They made the following statements: “The results of this study do not support the conventional theory that malignant tumors of the testis usually arise from teratomas.” and “If teratoma has no histologically recognizable malignant components, the qualified designation ‘adult’ is justified; the term ‘benign’ should never be used, because metastasis of testicular tumors which appeared to be only adult teratomas has occurred.” Friedman and Moore proposed a new model where the initial event in the testis was the development of a primitive germ cell tumor (i.e. – embryonal carcinoma), which then differentiated into teratoma. At that time they considered seminoma and “end stage” neoplasm, which turns out to be incorrect. As is mostly the case, progress in science and medicine is made in increments rather than in total.

Over the course of years, additional evidence is generated that supports the viewpoint of Friedman and Moore concerning testicular teratomas: the postpubertal teratomas are found to be aneuploidy, mostly in the hyperdiploid to hypotriploid range, and consistently associated with germ cell neoplasia in situ (GCNIS), (previously known as intratubular germ cell neoplasia, unclassified type); the teratoma components of mixed germ cell tumors have similar cytogenetic and molecular findings as the associated primitive germ cell tumors (supporting derivation of the former from the latter); and teratomas are discovered to have chromosome 12p amplification (including isochromosome 12p).

As these observations concerning postpubertal testicular teratomas were being made, other investigators were studying the much less common prepubertal cases. Perhaps unexpectedly these neoplasms showed an entirely different profile. The prepubertal teratomas were found to be entirely diploid, to have normal karyotypes, to lack 12p amplification (including i(12p)), mostly occurred as pure tumors without a primitive germ cell tumor component, were not associated with GCNIS and were always benign.

In 1973 Mostofi and Price explicitly stated what Friedman and Moore had shown almost 30 years previously: “Although no malignant areas may be identified, teratoma should not be designated as benign.” In the 1980s the recognition that the pediatric teratomas are different and benign is incorporated into standard textbooks of oncology. The “terminally differentiated” concept of seminoma also began to be challenged in that decade. In 1988 Srigley et al published an ultrastructural study of seminomas that showed a subset with what was described as “early carcinomatous differentiation” represented by distinct epithelial features including well-formed
desmosomes. This supported the transformation of seminoma to embryonal carcinoma and other forms of non-seminomatous tumor and led to the “tetrahedron model” of testicular germ cell tumor histogenesis, with seminoma a pivotal entity that gave rise to various other germ cell tumor subtypes. Ploidy studies, showing a consistently higher DNA content in seminomas compared to the non-seminomas,\textsuperscript{13,14} quickly ensued and supported this concept, as did studies showing parallel gains and losses of certain chromosomes in seminomas and the associated non-seminomas of mixed germ cell tumors.\textsuperscript{15} Morphologic transition of seminoma to yolk sac tumor was documented in 1992.\textsuperscript{16} Ultimately these and similar observations provided evidence that a teratoma in the postpubertal testis represented terminal differentiation of a primitive germ cell tumor rather than, as was the belief in Ewing’s era, that teratoma was the initial event. This sequence explains why postpubertal teratomas of the testis are highly associated with GCNIS, are uncommon as pure tumors, and also their association, even when seen as a pure tumor in the testis, with metastases of non-teratomatous germ cell tumor types, a situation reflecting dissemination of the precursor prior to its spontaneous regression in the testis.

While these observations concerning testicular teratomas were evolving, work concerning ovarian teratomas showed a much different situation. In 1969 Dr. David Linder showed that patients whose normal tissues were heterozygous for certain isoenzymes had dermoid cysts of the ovary that were consistently homozygous for those isoenzymes.\textsuperscript{17} In 1975 Linder et al essentially demonstrated the same phenomenon at the DNA level by showing that the dermoid cysts of patients who were heterozygous for polymorphic alleles of certain genes were always homozygous for those alleles.\textsuperscript{18} Later studies confirmed and refined these findings in microdissected specimens that avoided contamination of teratoma with host tissues.\textsuperscript{19} These observations supported that mature cystic teratomas of the ovary arose as true parthenogenetic neoplasms from a postmeiotic I - premeiotic II germ cell. In contrast to the postpubertal testis, there was no derivation from a primitive germ cell tumor. Ovarian teratomas, unlike testicular, derived from a benign germ cell; when malignant transformation occurred in ovarian teratomas it was a post-teratomatous event, most commonly in the form of squamous cell carcinoma, and analogous to malignant change at any somatic site. Noumoff et al provided support by showing the same marker chromosomes in the benign and malignant components of an ovarian teratoma.\textsuperscript{20} This, with previously mentioned considerations, leads to the following model of germ cell tumor histogenesis:
As satisfying as some aspects of this model are for aiding our understanding of teratomas and germ cell tumor histogenesis, it is clearly not complete. Uncommonly, mixed germ cell tumors with teratoma components occur in the ovary. It would be logical to believe that they developed similarly to postpubertal mixed germ cell tumors of the testis; there is some evidence for this in that i(12p) and other forms of 12p amplification have been found in both the teratoma and primitive germ cell tumor components of these cases.\textsuperscript{21} So in this circumstance teratoma in the ovary may actually derive from a primitive germ cell tumor. Additionally, there is now some evidence that rare teratomas in the postpubertal testis develop in a fashion similar to ovarian or pediatric testicular teratomas and are entirely benign. We recently published our experience with these, reporting a total of 25 cases consisting of 10 testicular dermoid cysts and 15 non-dermoid teratomas with benign features.\textsuperscript{22} These occurred over a wide age range (12-59 years) but tended to cluster in patients in their teens and 20s, suggesting that at least some of them may be previously undetected teratomas that developed prepubertally. In contrast to the usual postpubertal teratomas, these were more organoid and tended to have prominent components of ciliated epithelium, smooth muscle and squamous epithelial-lined cysts. Furthermore they lacked the cytological atypia that is very frequently seen in the postpubertal tumors and occurred in a normal-appearing parenchyma without
any evidence of germ cell neoplasia in situ (GCNIS), also contrasting with the situation of the usual postpubertal teratomas. When investigated by FISH for 12p amplification, none was found, and the available follow-up in all of the cases was benign. These observations permitted expansion of the model of testicular germ cell tumor and teratoma histogenesis:

The extragonadal teratomas that characteristically occur in children have many similarities to prepubertal testicular teratomas and ovarian teratomas, but likely have a different pathogenesis. Whereas the gonadal teratomas originate from germ cells, an embryonic stem cell is the most likely source for the extragonadal teratomas. This hypothesis is supported by the work of Linder et al, who found that the extragonadal teratomas (sometimes with associated yolk sac tumors and mostly occurring in the sacrococcygeal region of infants) were heterozygous for alleles in patients whose normal tissue was also heterozygous. This contrasted with ovarian teratomas and did not support origin from a post-meiotic I – pre-meiotic II germ cell but rather derivation from a mitotic cell. Additional work showed that the pure teratomas had normal karyotypes and lacked any 12p amplification. It is only with the emergence of yolk sac tumor within them that karyotypic abnormalities occur, and yolk sac tumor elements characteristically are first seen quite focally and adjacent to immature neuroectodermal elements. Clinical studies have further shown that pure sacrococcygeal teratomas may recur as
yolk sac tumor. The most sensible way to put these observations together is that an embryonic stem cell initially forms teratoma and that some teratomas (the high grade immature ones) may progress to yolk sac tumor. So the order of development for teratoma is exactly opposite of that we discussed with the postpubertal testicular teratomas and actually conforms to the original model presented in Ewing’s textbook.

Mediastinal germ cell tumors display the whole spectrum of histogenesis and, accordingly, the finding of teratoma in this location has very different clinical implications that are critically linked to the age and gender of the patients. For this reason it is important to consider these tumors in separate categories by age and/or gender.

The mediastinal germ cell tumors in prepubertal children, while relatively uncommon, are entirely analogous to the sacrococcygeal tumors. First of all they are almost exclusively teratomas and/or yolk sac tumors, with the former predominating and the latter, when present, usually occurring focally. They occur in both males and females although, as in the sacrococcygeal cases, females predominate, especially if there is a yolk sac tumor component. Additionally the majority are in children 2 years of age and less, and it is exceedingly rare that other forms of germ cell tumor are identified in the mediastinum until puberty and beyond. The pure teratomas have normal chromosomal findings, but, when yolk sac tumor develops, gains and losses of certain chromosomal regions occur in a pattern identical to that seen in the sacrococcygeal tumors. The model proposed for the development of sacrococcygeal teratomas therefore applies, with an embryonic stem cell first forming teratoma and the occasional “dedifferentiation” of teratoma to form yolk sac tumor.

In postpubertal females, mediastinal germ cell tumors are overwhelmingly pure, mature teratomas, a situation very similar to that of the ovary. These have an entirely benign clinical course. They have not been studied, to the best of my knowledge, for homozygosity or heterozygosity of polymorphic genes, and the analogy with ovarian teratomas may well not apply to their cell of origin. When rare malignant germ cell tumors occur in postpubertal females, their features are similar to those tumors that occur in the mediastinum of similarly aged males, with germinomas predominating (see below).

In postpubertal patients, malignant mediastinal germ cell tumors occur almost exclusively in males and they exhibit the spectrum of morphologies that occur in the testis in this same age group, although the relative proportion of various types differs, with pure yolk sac tumors being more common and pure embryonal carcinomas and mixed germ cell tumors being less so. As in the testis, seminoma is the single most common
tumor in this group. A significant departure from the testis, however is the fact that the great majority of teratomatous elements in the mediastinum in postpubertal males occur in pure, mature tumors and these are benign. Teratoma may also occur in the context of a mixed germ cell tumor, and, as in the testis, commonly show cytological atypia. One therefore has to be quite careful regarding the diagnosis of mediastinal teratomas in postpubertal patients in specimens other than total resection because it may not be otherwise possible to determine if the sampled teratoma represents a portion of a pure, mature teratoma or one element on a mixed malignant germ cell tumor – the difference between a benign and malignant lesion. Furthermore one has to be cognizant of the fact that post-chemotherapy resections of previously treated mixed germ cell tumors may consist entirely of teratoma, but these are of the malignant type, and their persistence a reflection of their relative chemoresistance compared to the primitive germ cell tumors from which they derived.

References