Extended Abstract

Extended abstract: pathologic considerations concerning mediastinal germ cell tumors

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Mediastinal germ cell tumors (GCTs) have diverse features, and time does not allow for anything other than coverage of some key considerations in this brief talk. What I would like to emphasize is the importance of understanding that there are two pathogenetically different types of mediastinal GCT, and that the clinical and pathologic features of these two types are dissimilar. These differences become most evident in teratomas; hence, the talk will concentrate on those neoplasms, with some consideration of a few key properties of mediastinal yolk sac tumor (YST).

Primary anterior mediastinal GCTs are felt to originate within the thymus, with possible sources being a mismigrated primordial germ cell or a thymic stem cell. Isolated anterior mediastinal involvement by a GCT indicates a primary neoplasm (1); when it is accompanied by middle or posterior mediastinal or retroperitoneal disease, the anterior mediastinal tumor is likely a metastasis. In adults, GCTs represent about 15% of anterior mediastinal tumors, trailing in frequency thymic neoplasms and cysts (46%), lymphomas (23%), and endocrine tumors (16%) (2). In children, they are a greater proportion of anterior mediastinal tumors (24%) (2), although the overall number of cases is much less than in adults.

Oosterhuis and Looijenga (3,4) consider that there are two basic forms of anterior mediastinal GCT; type I, originating from a benign precursor cell and initially forming teratoma with the possible subsequent development of YST via dedifferentiation of teratoma; and type II, developing from a malignantly transformed precursor cell that subsequently gives rise to the familiar spectrum of GCT types (seminoma/germinoma, embryonal carcinoma, YST, choriocarcinoma, and teratoma). Malignant transformation, therefore, occurs after teratoma is formed in type I GCTs, and before any invasive GCT, including teratoma, is formed in the type II pathway.

Type I GCTs consist only of teratoma and YST, are the type children exclusively develop, also occur in adults, and lack the chromosome 12p overrepresentation of the type II GCTs. In children 58% are pure teratomas, and the remainder have a YST component, with or without teratoma (2). The hypothesis is that YST develops in type I teratomas from embryonic-type neuroectoderm, which is supported by the juxtaposition of these elements in type I mixed GCTs. Pure teratomas of the anterior mediastinum in women and a subset of those in men show similar features to those in children, and, like the pediatric teratomas, are benign (5). On histological examination, the teratomas lack cytological atypia and are often organoid, the latter often reflected by bronchus-like structures, pancreatic tissue containing lobules of acinar cells with associated ducts and embedded islets, or skin formation.

The type II GCTs occur almost exclusively in young, post-pubertal males, show a very high frequency in Klinefelter syndrome (estimated at 19-fold higher, with 22% of cases having Klinefelter syndrome), include the entire spectrum of GCT types, have consistent chromosome 12p overrepresentation, may progress to a somatic-type malignancy (i.e., sarcoma or carcinoma), and have a unique association with vascular neoplasia and hematopoietic malignancies of GCT origin (5-13). About 50% are pure seminomas followed by mixed GCTs and YST (14). The type II teratomas, unlike the type I, show cytological atypia, with mitotic figures, and are less frequently organoid (5). They may induce cystic change of thymic epithelium,

causing a confusing radiographic picture because teratomas also form cysts.

A virtually uniform property of mediastinal YSTs is epithelial-mesenchymal transition. This may be manifest as blastema-like aggregates of tumor cells adjacent to epithelial YST, followed by their transition to dispersed spindle cells in a myxoid stroma. The resulting loose meshwork represents the neoplastic homology of the extraembryonic mesoderm of the early blastocyst. Overgrowth of such foci to greater than 5 mm in diameter results in sarcomatoid YST (SYST) (15). Histologically, SYST shows spindled to epithelioid cells of varying cell density in a myxoid to fibrous stroma with curvilinear blood vessels. The spindled cells in such foci may progress to vasoformative cells, a not totally unexpected occurrence given that the homologous extra-embryonic mesoderm is both a vasculogenic and hematopoietic site. Thus, neoplastic blood vessels, with both atypical endothelial and smooth muscle components, are found admixed with non-differentiated spindle cells, a lesion designated as either vasculogenic mesenchymal stroma or vasculogenic mesenchymal tumor (VMT), depending on whether there is overgrowth in excess of a 5-mm diameter field (9). VMT in a post-chemotherapy resection has been shown to increase the risk for subsequent sarcoma, either angiosarcoma or other sarcomas (9). Furthermore, the presence of vasculogenic lesions in mediastinal GCTs is associated with an increased risk of death (11% *vs.* 1%; P=0.001) due to leukemia or myelodysplasia of GCT origin (9). This is because neoplastic hematopoiesis of germ cell origin occurs within vasculogenic lesions, either within the blood vessels or the intervening stroma (9,13). Type II GCTs of the mediastinum are prone to progress to sarcomas or carcinomas ("somatic-type" malignancies). While most observers attribute this phenomenon to "dedifferentiation" of teratoma, it seems probable that many cases of sarcoma develop from SYST. Furthermore, many apparent "adenocarcinomas" in this context have morphological and immunohistochemical evidence of glandular YST.

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