Histopathology and Biology of Testicular Germ Cell Tumor

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1. Introduction

The versatile histopathology, clinical presentation, and biologic behavior of testicular neoplasms reflect the complex composition of the male gonad. Each component can develop different tumor types; thus, there are testicular germ cell tumor (TGT), sex cord/stromal tumor, miscellaneous tumors arising from rete testis or paratesticular structures, and tumors not specific to testicular parenchyma, such as lymphoma or mesenchymal neoplasms. All these varieties pose a challenge to both pathologists and clinicians regarding their diagnosis and treatment.

2. Nomenclature

Nowadays, the most widely adopted classification is the 2004 World Health Organization (WHO) classification. The terminology of the 2004 WHO classification is essentially the same as the classification for ovarian tumors. However, one should bear in mind that the clinicopathologic features of testicular tumors are markedly different from those of ovarian tumors.

Other than the WHO classification, there are other terms that are no longer in use, such as “infantile embryonal carcinoma”, which refers to pediatric yolk sac tumor, and “endodermal sinus tumor”, which is also equivalent to yolk sac tumor. In 1976, a divergent classification was proposed by the British Testicular Tumor Panel, which intended to call most TGT as teratoma. However, the classification did not gain worldwide acceptance.

3. Relevance of Histopathologic Classification

The histopathologic classification of TGT is strongly associated with clinical features. In terms of age distribution, the incidence shows three age groups. In the infants and children, the majority of TGT are composed of yolk sac tumor and teratoma. In young adults in the third to fourth decade, seminoma and mixed germ cell tumors predominate. Testicular tumors in men older than 50 years have a high frequency of malignant lymphoma. Spermatocytic seminoma is a rare tumor, and almost all occurs in the elderly.

The histologic subtypes also reflect the degree of differentiation and correlate with biologic behavior in respect to benignity versus malignancy. In the pediatric group, yolk sac tumor is malignant while all prepubertal testicular teratomas are benign even with immature histology. On the contrary, all postpubertal TGTs are malignant, even those with “benign” histology (mature teratoma) still have metastatic potential. The teratoma is considered the most differentiated form, while the embryonal carcinoma the most dedifferentiated one. Hence, the proportion of different elements may influence the overall prognosis.

The different forms also dictate their metastatic route. Most of the TGT components metastasize to retroperitoneal lymph nodes through lymphatics; meanwhile, the choriocarcinoma is notorious for its hematogenous spread owing to its propensity to invade vascular system even when the tumor is small. Therefore, choriocarcinoma can skip the retroperitoneal lymph nodes before it develops widespread metastases.
The different subtypes correlate to the level of serum markers. Generally, the yolk sac tumor is associated with a high level of α-fetoprotein. The immature hepatenteric component in teratoma can also moderately elevate α-fetoprotein levels. The high level of human chorionic gonadotropin usually indicates the presence of choriocarcinoma or scattered syncytiotrophoblasts. All these tests can provide useful clues for diagnosis and postoperative surveillance.

Finally, the different histologic subtypes have implication regarding the responsiveness to adjuvant therapy. Generally speaking, the seminoma is radiosensitive, and patients with pure seminoma of low stage are able to achieve long-term survival. Other non-teratomatous TGT components are responsive to multimodal therapy and high remission rate can be accomplished. On the contrary, teratomatous component is non-responsive to chemotherapy and radiotherapy. Consequently, surgical excision is the only modality to extirpate teratoma.

4. Intratubular Germ Cell Neoplasia, Unclassified Type

When the tumor cells are confined in the seminiferous tubules, it is called intratubular germ cell neoplasia. Among the groups of intratubular germ cell neoplasia, the intratubular germ cell neoplasia, unclassified type (IGCNU) (formerly called carcinoma in situ) is considered a universal precursor of all testicular germ cell neoplasm except pediatric teratoma and yolk sac tumor, spermatocytic seminoma, and dermoid cyst. IGCNU should be discerned from other specific forms of intratubular germ cell tumor, such as intratubular seminoma, intratubular embryonal carcinoma or intratubular choriocarcinoma, which represent intratubular involvement of invasive TGT.

IGCNU is defined as presence of atypical cells resembling the cells of invasive seminoma and demonstrating a characteristic distribution around the perimeter of seminiferous tubule mingling with the non-neoplastic germ cells and the Sertoli cells (Figure 1). IGCNU has similar risk factors as invasive TGT, including cryptorchidism, infertility and gonadal dysgenesis syndromes. IGCNU also exhibits similar immunophenotype to that of seminoma, including placental alkaline phosphatase, CD117, OCT3/4, NANOG and SOX2. Ploidy evaluation of IGCNU cells demonstrate a range of hypotriploidy to hypopentaploidy, but the isochromosome 12p gain observed in invasive TGT is absent in IGCNU. Clinically, about 50% of cases with IGCNU progressed into an invasive TGT within 5 years after identification, and only a small fraction of patients remain free of an invasive tumor by 7 or 8 years of follow-up. These evidences lend further weight to the histogenetic role of IGCNU in TGT.

Figure 1 (A) Intratubular germ cell neoplasia, unclassified type, characterized by atypical cells lining at the basal portion of the seminiferous tubules. (B) The neoplastic cells can be highlighted by immunohistochemical stain for placental alkaline phosphatase.

Figure 2 Histogenetic model of testicular germ cell tumor. The intratubular germ cell neoplasia, unclassified type (IGCNU) is the initial step in the oncogenesis of postpubertal germ cells tumor except spermatocytic seminoma, while it is absent in the pediatric yolk sac tumor and teratoma. CC = choriocarcinoma; EC = embryonal carcinoma; IMT = immature teratoma; MT = mature teratoma; p-T = pediatric teratoma; p-YST = pediatric yolk sac tumor; S = seminoma; SS = spermatocytic seminoma; YST = yolk sac tumor.
A model of TGT histogenesis has been advanced recently (Figure 2). In the model, IGCNU plays a pivotal role as the first step of malignant transformation in adult TGT (except spermatocytic seminoma and dermoid cyst). When IGCNU acquires further mutation (e.g., isochromosome 12p gain), it differentiates into various forms of TGT and mature teratoma is the most differentiated form. The model can explain many paradoxical behaviors of TGT. Since the tumors in the primary site and different metastatic sites can differentiate into different forms, it is not surprising that the histology of metastatic tumor can differ from that of the primary tumor.

In contrast to most of adult TGT, the pediatric yolk sac tumor, pediatric teratoma, spermatocytic seminoma and dermoid cyst do not have IGCNU as precursor. Therefore, different mechanisms are involved in the histogenesis of those tumors. It also explains that these groups of tumor usually histologically manifest as pure form and have a more homogenous biologic behavior than that of adult TGT.

5. Extragonadal Germ Cell Tumor

Genuine germ cell tumors can arise in extragonadal sites, including the pineal region and mediastinum. However, it should be noted that many retroperitoneal germ cell tumors represent metastases from an occult or burn-out, spontaneous regressed, primary TGT. In this clinical context, the absence of a palpable mass within the testis is insufficient to exclude its presence. Also, IGCNU may be found in the testes of patients of clinical extragonadal germ cell tumor, more commonly in the retroperitoneum than the mediastinum. If the possibility of metastatic germ cell tumor can be definitively excluded, the germ cell tumors arising in the pineal region and mediastinum may represent a true extragonadal counterpart. These “true” extragonadal germ cell tumors are not related to IGCNU, and their biologic behavior is determined by histology and genetic alteration.

6. Conclusion

The management of TGT is a paradigm of cooperation between the clinician and pathologist. Ultimate treatment is achieved with thorough clinical evaluation and complete pathologic examination. It is of utmost importance for clinicians to understand the terminology of TGT and its clinical relevance to tailor a satisfactory treatment and surveillance protocol for patients with TGT.

References