Peripheral Neuroblastic Tumors (神経芽腫群腫瘍) の病理

Professor of Clinical Pathology, Children’s Hospital Los Angeles University of Southern California Keck School of Medicine
Hiroyuki Shimada, M.D., PhD.

Peripheral Neuroblastic Tumors (pNTs: Neuroblastoma, Ganglioneuroblastoma, Ganglioneuroma), derived from neural crest cells and diagnosed in adrenal medulla and paraspinal ganglia, are the most common non-CNS tumors in children. Approximately 700 cases are newly diagnosed in US every year. pNTs are genomically complex disease, and offer one of the best models for analyzing biologically significant relationship between molecular/genomic alterations and their morphologic manifestations.

International Neuroblastoma Pathology Classification (INPC), established in 1999 and partly revised in 2003, is a morphologic classification designed to be prognostically significant and biologically relevant. The INPC defines the age-appropriate framework of sequential tumor differentiation/maturation and mitotic/karyorrhectic activities based on the phenotypical manifestations of three major biologic factors: (A) Cross talk between neuroblastic cells and Schwannian stroma cells essential for tumor maturation from Neuroblastoma (Schwannian stroma-poor) to Ganglioneuroblastoma-intermixed (Schwannian stroma-rich) to Ganglioneuroma (Schwannian stroma-dominant) category; (B) trkA (high-affinity NGF) expression critical for neuroblastic differentiation (3 subtypes defined: undifferentiated, poorly differentiated, and differentiating) in Neuroblastoma category; and (C) MYCN amplification as the powerful driving force for preventing neuroblastic differentiation and promoting mitotic and karyorrhectic activities (3 classes of MKI – mitosis-karyorrhexis index - defined: low of <100/5,000 cells, intermediate of 100–200/5,000 cells, and high of >200/5,000 cells) in Neuroblastoma category. Besides Neuroblastoma, Ganglioneuroblastoma-intermixed, and Ganglioneuroma, there is a fourth category of Ganglioneuroblastoma-nodular (composite, Schwannian stroma-rich/stroma-dominant and stroma-poor) where Neuroblastoma tumor nodule is coexisting with either Ganglioneuroblastoma-intermixed or Ganglioneuroma. According to the INPC, each case of pNT is classified into one of two prognostic groups, Favorable Histology group (within the age-appropriate framework of tumor differentiation/maturation and mitotic/karyorrhectic activities) and Unfavorable Histology group (outside the framework).

COG (Children’s Oncology Group) Neuroblastoma Biology Study has established a risk grouping scheme, based on the combination of prognostic factors (age at diagnosis, clinical stage, INPC, MYCN status, DNA index, 1pLOH, and unbl1qLOH). With this scheme, patients are assigned to low- (projected 5-year EFS of >95% with surgery alone), intermediate- (EFS of >90% with surgery/biopsy and chemotherapy), or high-risk groups (EFS of ~40% with intensive treatment including BMT) for further clinical trials. Historically the COG studies have been successful in eliminating/reducing unnecessary chemotherapy/irradiation therapy for those patients in the low- and intermediate-risk group without decreasing the survival rates. As for patients in the high-risk
group, however, trend of improving the survival has started to level off in recent years in the face of increasing or almost maximizing therapy intensity. Even disturbingly, we are experiencing significant morbidity in survivors after intensive chemoradiotherapy.

Continuous improvement of survivals, especially for those patients in the high-risk group, could only be possible with more precise understanding of the biology, leading us to specific treatment targets, of this disease: Recent success of anti-GD2 treatment after myeloablative therapy as well as 131I-labeled MIBG radiotherapy, and potential inclusion of Aurora kinase inhibitors in therapeutic regimen are the examples. However, still a huge work should be expected in this field. For example, pNTs are well known to have various chromosomal gains (1q, 2p, 5q, 17q, 18q) or losses (1p, 3p, 4p, 9p, 11q, 14q, 15p, 19q) without clearly identified or defined responsible genes except MYCN mapped to 2p24. Discovery of ALK mutation in familial neuroblastoma cases as well as approximately 15% of sporadic cases also gives us a new insight of this disease.

Our progress in pNT research would only be assured by multi-disciplinary collaboration by oncologists, surgeons, radiologists, biologists, immunologists, statisticians, nurses, and advocates, etc., nationally and internationally. We pathologists will play the critical role in the translational research by not only providing the standardized diagnostic review and prognostic evaluation, but also bridging between laboratory bench and bedside.