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Keynote Lecture 1

Small round ceil tumors. A challenge for surgical pathology: Past and future

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For clinical oncologists Ewing's sarcoma has been known for years as a very rare tumor of infancy and childhood affect¡ng bone. Previously, only pediatricians and children-oriented pathologists were actually interested in this malignant disease. However, the disease has recently attained dramatically wide interest for several reasons.

The tumor appears not only in bone, but also in soft tissues, and even more extraordinarily in solid organs and in skin; the neoplasm is limited not only to the pediatric group, but also extends to adults. The morphological characterization of the neoplasm has become a challenge for pathologists involved in routine diagnostic procedures. New techniques, such as electron microscopy and immunohistochemistry, are considered to be mandatory for their diagnosis, and histogenesis of the tumor is still a matter of controversy. Current biological techniques, such as tissue culture, cytogenetics, and molecular biology, have generated new insights into the real nature of the neoplasm. Specific genetic abnormalities have led to the discovery of Ewing's sarcoma-associated gene rearrangements, which in turn have led to the recognition of several categories of tumors, thus transforming °a unique neoplasm" into "a family of tumors". The categorization of the chimeric gene product resulting from the chromosomal transiocation (see gene fusions> produces a Ewing's sarcoma-derived oncoprotein, which provides a novel model of carcinogenesis and thus, a system to study malignant transformation at a laboratory level that could prove of clinical use for prognosis and therapy.

At present, nearly 60% of such patients are cured with multimodal therapy, but over 80% of cases with metastatic disease succumb within a 5-year period. Therefore, the cure for this neoplasm awaits further findings from the laboratory, and the distinction between low and high grade Ewing's sarcoma still evades prognostic studies.

Therefore, the oíd Ewing's sarcoma tumor" concept, now the Ewing's sarcoma family of tumors", is an example of the evolution of pathology in the present century, and sets the path for new insights into the identification of the role and the challenges of pathology in the coming century.

What will be discussed here is not only an exotic example of tumoral biology, but also a model for many other neoplasms arising in the human being, and what the pathologist will have to face in future regarding its clinical practice.

Historical perspectives of Ewing's sarcoma

Several periods will be considered in this review:

i) Pathology in the early years of this century: James Ewing (US) and Charles Oberling <France);
ii) The transition period of World War ll: Arthur Purdy Stout and Friz Schajowicz;
ii) Electron microscopy (a new tool for pathology): early studies on Ewing's sarcoma;
iv) The immunohistochemistry period: from HNK-1 to Mic-2 (CD57 to CD99);
y) Cytogenetics and molecular biology applied to surgical pathology: from molecular biology laboratories to the pathologist's bench. Cytogenetic translocations t(11;22)(q12;q24) and gene rearrangements (EWS-FLI1; EWS-ERG);
vi> Challenges for the new era: from the globalization of pathology to the limits of histopathology.

Diagnostic tools in surgical pathology

Some of the diagnostic tools which have helped to formulate the Ewing's sarcoma concept include:

i) Conventional histological techniques: glycogen staining (periodic acid-Schiff amylase, Best's carmin);
ii) Enzyme histochemistry; electron microscopy (transmission + scanning); immunohistochemistry, neural markers; tissue cultures – celí modulation or celí heterogeneity, antibodies overexpression, morphological reorganization;
ii) Xenografts: nude mice grafting, morphological and biological features;
iv) Cytogenetics: main chromosomal translocations, first and second mutations;
y) Molecular biology: genetic rearrangement, types of ETS family of tumors;
vi) Ewing's sarcoma: a family of ETS tumors with complex microscopic similarity.

Histogenetic evolution of the Ewing's sarcoma concept

The following highlights the evolution of this concept, a matter which is still under debate:

i) Ewing's sarcoma is a hemangioendothelioma of bone (1920);
ii) Ewing's sarcoma is a mesenchymal sarcoma of bone (1940);
ii) Ewing's sarcoma is a primitive sarcoma of bone and soft tissue (1970);
iv) Ewing's sarcoma is related to peripheral neuroepithelial lesions but not to neuroblastoma (1980);

v) Ewing's sarcoma belongs to a family of primitive neuroectodermai tumors located in bone, soft tissue and visceral organs (1990);

vi) The EWS gene belongs to a family of ETS transcription factors with more than 30 markers (1995);

vii) The identification of the EWS-ETS target genes and their mechanism of malignant conversion are still enigmatic and the precursor cell of the tumor not known (2000).

New challenges for pathologists

Based on the former considerations, the following questions arise:

i) Is the histopathological diagnosis no longer based upon morphological features exclusively?

ii) Has it been usurped by studies that until now were considered ancillary?

ii) Is there a given panel of antibodies that a pathologist must follow in a given tumoral entity to assure the histological diagnosis?

iv) In such a case, is failure to follow this to be considered an error in the standard practice of pathology?

v) Should all undifferentiated neoplasms be submitted to electron microscopy? Is this standard of practice in the pathology laboratory?

vi) Is it the standard of practice in a laboratory to reach the correct diagnosis in 100% of cases?

vii) Is a pathologist obliged to accept the diagnosis of a second consulting pathologist?

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