CYTOHISTOLOGY OF THE SEROUS MEMBRANES

CYTOHISTOLOGY OF SMALL TISSUE SAMPLES

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Edited by

Claire W. Michael, MD

Professor of Pathology, Case Western Reserve University/University Hospitals Case Medical Center, Cleveland, OH, USA

David C. Chhieng, MD, MBA, MSHI

Professor of Pathology and Director of Cytology, Mount Sinai Icahn School of Medicine, New York, USA

Carlos W. M. Bedrossian, MD, FIAC

Professor of Pathology, Rush University Medical College and Medical Director, Biomedical Concepts, Chicago, IL, USA

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Claire Michael

To my parents William and Nawal for their unconditional love and inspiration
To my husband Raouf for his continuous support

and

To my mentor Carlos Bedrossian for instilling in me the love of cytology
and to whom I credit my career success.

David Chhieng

To my parents and my partner Stephen

Carlos Bedrossian

To my wife, Ana Maria dos Reis Campos for her unwavering support
To my children Vanessa, Richard and Robert who might (or then again might not. . .)
have missed having daddy around while he was pursuing his career.

and

To the memory of my parents Hovanes and Aparecida who instilled in me the love of learning.

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CONTRIBUTORS

Adebowale J. Adeniran
Department of Pathology, Yale University School of Medicine, New Haven, CT, USA

Sarah M. Bean
Department of Pathology, Duke University Medical Center, Durham, NC, USA

Carlos W. M. Bedrossian
Rush University Medical College and Biomedical Concepts, Oak Park, IL, USA

Guoping Cai
Department of Pathology, Yale University School of Medicine, New Haven, CT, USA

David C. Chhieng
Department of Pathology, Mount Sinai Icahn School of Medicine, New York, USA

Katalin Dobra
Karolinska Institute, Stockholm, Sweden

Anders Hjerpe
Karolinska Institute, Stockholm, Sweden

Jeffrey T. Jhee
Biomedical Concepts, Oak Park, IL, USA

Xin Jing
Department of Pathology, University of Michigan Health System, Ann Arbor, MI, USA

Qing Kay Li
Department of Pathology, Johns Hopkins Bayview Medical Center, Baltimore, MD, USA

Stewart M. Knoepp
Integrated Health Associates, St. Joseph Mercy Health System, Ann Arbor, MI, USA

Adhemar Longatto-Filho
Life and Health Sciences Research Institute, School of Health Sciences, University of Minho, Braga, Portugal; ICVS/3B'S_PT Government Associate Laboratory, Braga / Guimasães, Portugal; Medical Investigation 14, Faculty of Medicine, University of São Paulo, São Paulo, Brazil, Molecular Oncology Research Center, Barretos Cancer Hospital, PioXII Foundation, Barretos, Brazil

Claire W. Michael
Department of Pathology, Case Western Reserve University/University Hospitals Case Medical Center, Department of Pathology, Cleveland, OH, USA

Filip Mundt
Karolinska Institute, Stockholm, Sweden

Aziza Nassar
Department of Pathology, Mayo Clinic, Jacksonville, FL, USA

Michael H. Roh
Department of Pathology, University of Michigan Health System, Ann Arbor, MI, USA

Fernando Schmitt
Institute of Molecular Pathology and Immunology, Medical Faculty of Porto University, Porto, Portugal, and Laboratorie national de santé, Luxembourg

Berrin Ustun
Department of Pathology, Albert Einstein College of Medicine of Yeshiva University, Bronx, NY, USA

INTRODUCTION

As part of the PSC's *Cytohistology of Small Tissue Samples* monograph series this book is intended for use in the daily practice of pathology when evaluating cytological specimens and small tissue samples of the serosal membranes. Neither an atlas nor a textbook, the text and the illustrations emphasize the indivisible nature of cytological and histological features of mesothelium-lined structures which allow their recognition as normal or abnormal. The term cytohistology is not used loosely but precisely chosen to emphasize cyto-histological correlation as the scientific basis for the pathological diagnosis of disease conditions since the time of Virchow, through the era of Koss, and gazing beyond the horizon toward the time when digital microscopy and far-flung biomarkers may enjoy their heyday. Steeped on the cell theory Virchow identified cells as the site of disease and Koss, more than any of his contemporaries, drove home the concept that cellular samples faithfully reflect the underlying tissue abnormalities of the organs from which they derive. Thus, cytopathology complements histopathology and vice versa. Or put another way, the basic approach of this monograph is that a cell is a biological entity whereas tissue is a concept, an intermediate organizational level between the cell and another biological entity, the organ. As such, the pathologist cannot ignore the fact that the way cells relate to one another as much as cellular alterations, play a pivotal role in the recognition of disease. This book contends that this could not be better illustrated than in a mesothelial cell population. Inclusive, rather than exclusive in its approach, the book emphasizes how artificial it would be to pitch cytopathology and histopathology as separate from one another, in detriment to their eclectic integration in the era of cost containment and more customized medicine.

According to this monograph the serosal cavities, interconnected as they are to each other represent a complex and unique micro-environment within which pathological processes occur. The central premise of this book is that, not unlike an organ or a system, the serosal membranes constitute the functional grouping of multiple tissues, of which the mesothelium is the most significant, but by no means its only component. The subserosal layer also participates intimately in the mesothelial response to injury although its exact role in the development of neoplasms remains elusive. Throughout this book we do not treat static mesothelial cell changes as the sole manifestation of an underlying abnormality but present them as part of dynamic complex of alterations involving various cell types. For this reason we recommend repeating diagnostic taps and examining rather than discarding therapeutic taps in order to establish the temporal evolution of a disease process to facilitate its recognition. When evaluating an effusion specimen one must look at all possible clues, from the amorphous substances present in the background of the preparation, the cellularity and "demographics" of the cell population, the intercellular arrangements among the cells of interest, the architectural structures of the cell aggregates all the way to the individual cell morphology, including its outer surface, cytoplasmic contents and nuclear configuration. These features are described and illustrated as observed in routinely, Papanicolaou and Diff-Quik™-stained conventional smears, cytospins and LBC preparations as well as H&E and histochemical-stained cell blocks, invariably also immuno-stained with a panel of antibodies.

In chapters arranged as common, uncommon and rare neoplasms, rather than by organ systems, key features are illustrated to aid in the recognition of metastatic tumors, with separate chapters dedicated to carcinoma of unknown primary (CUP) origin and hematopoietic malignancies. Two separate chapters, one on molecular analysis of cells in serous fluids another on noninvasive biomarkers in the diagnosis and prognosis of malignant mesothelioma, illustrate the speed with which translational medicine is bringing novel discoveries into clinical practice. These and two additional chapters covering mesothelial response to injury and benign conditions of the serous membranes emphasize how cytological evaluations must be correlated horizontally

all the way to epidemiological, clinical and radiological imaging data, as well as to the sampling method, collection media, and the transport and handling of the specimen in the laboratory. This requires a close interaction with internists, oncologists, surgeons and their staff, interventional radiologists, pulmonologists and ultrasound specialists, as well as hospital personnel involved in specimen transportation, and the cytotechnologists that process the samples and examine them under the microscope. But the book also stresses how these evaluations must be extended vertically, from light microscopy with routine and special stains, through the immuno-histochemical detection of gene products with phenotypical significance to various ancillary techniques, judiciously selected according to the clinical questions being addressed including molecular testing for the diagnosis, prognosis and therapeutic choices. While acknowledging the added value represented by these novel applications of cytopathology, a detailed description of their utilization is beyond the scope of this book.

Although each chapter varies according to its specific topic, they all provide an overview of benign and malignant conditions which may or may not be readily diagnosed in small cytohistological samples. Advantages and limitations of each sampling method include not only inherent diagnostic data, but also clinical ease, speed and complications of one versus another, which will help cytopathologists in their interaction with clinical colleagues as well as shed light on how well we do in various disease conditions. To the extent possible, this includes accuracy, precision, diagnostic sensitivity, specificity, and positive and negative predictive values for various but not all sample types and different pathologic entities. When dealing with rapid onsite evaluations (ROSE) comparison is made between immediate smears and touch preps of CNB, and frozen sections whenever the data is available. Ending each chapter with a short series of variably comprehensive "case reports", provides a valuable take home teaching message as well as a blueprint on how to work-up classical as well as challenging conditions according to a properly formulated differential diagnosis. To our knowledge this is the first book to apply the recently issued guidelines for the cytopathological diagnosis of malignant mesothelioma from the International Mesothelioma Interest Group, also endorsed by the International Academy of Cytology and the Papanicolaou Society of Cytopathology.

While certain types of cytological samples are dwindling, serous fluids remain the most common type of non-gynecological specimens examined in the laboratory, accounting for anywhere between 180,000 to 200,000 samples annually in the U.S. alone. With the relative increase of cancer in comparison to other receding chronic diseases, the non-invasive, low-morbidity nature of harvesting cells from the serous membranes under image guidance, and the increasing repertoire of genetic and molecular testing now on the market, augur well for the future of FNA and CNB of the chest. Peritoneal and pelvic washings, are more commonly submitted for cytological evaluation than pleural washings, but this may change if a marker for early mesotheliomatous neoplasia is discovered. Serosal washings are covered in an introductory chapter, dedicated to the mechanism of pleural fluid formation as well as non-cytological techniques, including physical, biochemical, and bacteriological evaluation of serous effusions. The pleura, however, can be sampled during both closed (blind or image-assisted) and open (VATS or thoracotomy) lung biopsies which are covered in its own chapter. Throughout the book they are compared to minimally invasive cytohistological techniques, such as transcutaneous fine needle aspiration (FNA) and core needle biopsy (CNB), which along with vastly improved new sampling modalities can be considered an extension of the physical exam to the cellular level. These include endoscopic ultra-sound, trans-bronchial needle aspiration (EUS-TBNA) and flex-rigid pleuroscopy with fluorescent "smart probes" that provide real-time, delineation of both normal and neoplastic tissue and are gaining acceptance in the evaluation of cytology negative pleural effusions as well as the staging of intrathoracic neoplasms.

Intended neither as a comprehensive account of the cytohistology in every disease nor as an exhaustive review of every ancillary technique applicable to small serosal tissue samples, this book combines the illustration of time honored cytohistological clues with newly developed conceptual understandings made possible by progress in cytogenetics and molecular biology. Obviously, clear instances where ancillary techniques play a major role in uncovering new information of diagnostic, prognostic and therapeutic significance are described and illustrated in the chapter corresponding to the affected organ system. But ultrastructural studies are mainly restricted to the chapter on malignant mesothelioma where they are most helpful in elucidating the nature of light microscopic alterations. Effort was made to present high quality illustrations depicting a balanced mix of typical examples and rare variants of the same condition, so that the book should be of interest to recently graduated practitioners as well as the

experienced pathologist with an interest in this topic. Any author should be proud of publishing a book with two young, bright colleagues, one a former trainee, another a longtime friend. I am no exception. If we are successful in getting across our clinically integrated approach in the practice of cytopathology of the serous membranes and contributing towards its growing relevance, much credit belongs also to our collaborators who wrote excellent chapters and to a number of people who helped our endeavors in so many ways. To all of them I offer my heartfelt thanks.

CARLOS W. M. BEDROSSIAN