Cytopathology of the Glandular Lesions of the Female Genital Tract

Matías Jiménez-Ayala  Madrid
Beatriz Jiménez-Ayala Portillo  Madrid

Including contributions by

Francesc Alameda  Barcelona
Carmen Alvarez-Santín  Montevideo
Belén Lloveras  Barcelona
Dina R. Mody  Houston, Tex.
Ritu Nayar  Chicago, Ill.
Manuel Nevado Santos  Madrid
Lara Pijuán  Barcelona
Fernando Pinedo Moraleda  Madrid
Maria Carmen Rodríguez Alvarez  Montevideo
Volker Schneider  Freiburg
Adela Sica  Montevideo
Michael Thrall  Houston, Tex.

170 figures, 168 in color, and 26 tables, 2011
To Sara, for her family ‘sacrifices’ during her first 2 years of life and in the hope she will be the third step in our cytopathology saga.
Contents

XIII Preface
XIV Foreword
XV List of Abbreviations
XVI List of Authors

Chapter 1
Cytopathological Techniques for the Diagnosis of Glandular Lesions of the Genital Tract
1 1.1. Introduction
1 1.2. Fixation
2 1.3. Staining
3 1.4. Special Techniques
4 References

Chapter 2
2001 Bethesda System Classification of Glandular Lesions on Cervical Cytology
5 2.1. Introduction
6 2.2. Glandular Epithelial Cell Abnormalities
   6 2.2.1. Atypical Glandular Cells
   6 2.2.2. Atypical Endocervical Cells
   7 2.2.3. Atypical Endometrial Cells
8 2.3. Endocervical Adenocarcinoma in situ
9 2.4. Adenocarcinoma
12 2.5. Other
   12 2.5.1. Endometrial Cells in Women ≥40 Years of Age
13 2.6. Impact of the 2001 Bethesda System
13 2.7. Management
14 References

Chapter 3
Cytopathology of the Benign Glandular Lesions of the Cervix and Glandular Cytopathology of the Vagina
15 3.1. Cytopathology of Benign Glandular Lesions of the Cervix
   15 3.1.1. Benign tumors
3.1.1. Endocervical Polyp
3.1.2. Müllerian Papilloma
3.1.2. Other Non-Tumoral Lesions
3.1.2.1. Tubal Metaplasia
3.1.2.2. Microglandular Hyperplasia
3.1.2.3. Cells of the Lower Uterine Segment
3.1.2.4. Endometriosis
3.1.2.5. Arias-Stella Reaction
3.2. Glandular Cytopathology of the Vagina
3.2.1. Tumoral Lesions
3.2.1.1. Benign Tumoral Lesions: Adenomas
3.2.1.2. Malignant Tumoral Lesions: Adenocarcinomas
3.2.1.2.1. Clear Cell Adenocarcinoma
3.2.1.2.2. Endometrioid Adenocarcinoma
3.2.1.2.3. Mucinous Adenocarcinoma
3.2.1.2.4. Mesonephric Adenocarcinoma
3.2.2. Non-Tumoral Lesions
3.2.2.1. Adenosis
3.2.2.2. Fistulous Tracts
3.2.2.3. Tubal Prolapse
3.2.2.4. Post-Hysterectomy Glandular Cells

Chapter 4

Cytopathology of Adenocarcinoma in situ of the Endocervix and Its Differential Diagnosis

4.1. Introduction
4.2. Normal Endocervical Mucosa
4.3. Benign and Reactive Changes
4.4. Adenocarcinoma in situ
4.5. Clinical Management of AIS
4.6. Microinvasive Adenocarcinoma
4.7. CIN 3 Mimics AIS
4.8. Pregnancy Changes
4.9. The Vaginal Cuff

Chapter 5

Cytopathology of the Malignant Invasive Lesions of the Endocervix

5.1. Introduction
5.2. Types of Malignant Invasive Lesions of the Endocervix
5.3. Invasive Endocervical Adenocarcinoma
5.3.1. Early Invasive Adenocarcinoma
5.3.2. Mucinous Adenocarcinoma
5.3.2.1. Endocervical Type Adenocarcinoma of the Endocervix
5.3.2.2. Intestinal Variant
5.3.2.3. Signet-Ring Cell Variant
5.3.2.4. Minimal Deviation Variant
5.3.3. Villoglandular Adenocarcinoma
5.3.4. Endometrioid Adenocarcinoma of the Cervix
5.3.5. Clear-Cell Adenocarcinoma
5.3.6. Serous Adenocarcinoma
Chapter 10

**Glandular Lesions of the Fallopian Tube**

- 10.1. Histology of the Fallopian Tube
- 10.2. Benign Fallopian Tube Lesions
- 10.3. Tumors of the Fallopian Tube
  - 10.3.1. Benign Epithelial Tumors
  - 10.3.2. Malignant Epithelial Tumors
  - 10.3.3. Borderline Epithelial Tumors
  - 10.3.4. Carcinoma in situ
- 10.4. Diagnosis of Tubal Carcinoma
  - 10.4.1. Cytology
  - 10.4.2. Cytological Features
- 10.5. Differential Diagnosis

References

Chapter 11

**Metastatic Glandular Lesions**

- 11.1. Introduction
- 11.2. Metastases to the Genital Tract
  - 11.2.1. Metastases to the Vulva
  - 11.2.2. Metastases to the Vagina
  - 11.2.3. Metastases to the Cervix
  - 11.2.4. Metastases to the Endometrium
  - 11.2.5. Metastases to the Ovary
- 11.3. Origin of Metastases
  - 11.3.1. Intragenital Metastases
    - 11.3.1.1. Metastases of Ovarian Origin
    - 11.3.1.2. Metastases of Endometrial Origin
  - 11.3.2. Extragential Metastases
    - 11.3.2.1. Breast carcinoma
    - 11.3.2.2. Gastrointestinal Tract
- 11.4. Clues for the Diagnosis of Metastatic Carcinomas in Cervicovaginal Smear

References

Chapter 12

**Ancillary Techniques for the Diagnosis of Glandular Lesions of the Female Genital Tract**

- 12.1. Introduction
- 12.2. HPV Probe
  - 12.2.1. Hybrid Capture II
  - 12.2.2. PCR
- 12.3. Immunohistochemical Techniques for p16
- 12.4. Other Techniques
- 12.5. Conclusion

References

Index
Preface

Following our first publication in the Karger series *Monographs in Clinical Cytology* (vol. 17), which was devoted to endometrial adenocarcinoma, we have spent the last 2 years preparing this second volume, *Glandular Lesions of the Female Genital Tract*. We have been supported in this by series editor Dr. Svante Orell and Karger Publishers. The subject is an area in which we have wide experience and, on this occasion, we have been honored to welcome contributions from 12 international experts in the cytopathology of glandular lesions. Their writings cover the wide spectrum of this challenging subject.

Genital glandular lesions, both benign and malignant, are an attractive area of cytopathology. Malignant lesions of the endocervix and endometrium are becoming more common all the world, compared to squamous cell carcinoma. In this volume we present discussions of in situ and invasive endocervical adenocarcinoma, endometrial adenocarcinoma and endometrial hyperplasias.

Ovarian lesions focusing data obtained from intraoperative studies are considered. Other areas of the genital tract, such as the vulva and the fallopian tube, which are less common and thus have seen fewer publications, are also presented. The impact of the Bethesda System and basic and ancillary techniques in the study of glandular lesions complete our monograph.

We hope that this monograph will be useful to cytopathologists, pathologists, cytotechnologists and to students of these specialities, as it deals with the most common areas of their daily work.

Acknowledgements

Our gratitude goes to Dr. Svante Orell and to Mr. Thomas Nold for their stimulating discussions and help in the preparation of this book. Thanks also to the contributors and to the staff of the Instituto Jiménez-Ayala, with special mention to Paloma Fernandez Rueda for her dedicated and efficient secretarial work, and to senior cytotechnologist Concha Chinchilla.

Matías Jiménez-Ayala, FIAC. Instituto Jiménez-Ayala and Former Chair, Department of Cytology, Hospital Universitario Gregorio Marañón, Madrid, Spain
Beatriz Jiménez-Ayala Portillo, MIAC. Director, Instituto Jiménez-Ayala, Madrid,
Foreword

Glandular lesions of the female genital tract have always been a challenge for pathologists. The precise cytological diagnosis of these lesions is difficult because of their inherent complexity, as well as the lack of experience of many cytopathologists in this field.

This monograph brings to us an extensive review of the different glandular lesions of the female genital tract that can be recognized on cytological material. Through the different chapters, many authorities in the area show, in a very didactic way, the morphological criteria and the main differential diagnosis of several glandular lesions that will be very useful for pathologists and cytopathologists in daily practice. The 12 well-organized chapters also cover important topics in the area, such as routine and ancillary techniques for the diagnosis of glandular lesions and the 2001 Bethesda System classification of glandular lesions on cervical cytology. There are 170 figures, 168 in color, most of them of excellent quality – an important point in books dealing with morphological criteria for diagnosis. The 351 references distributed throughout the book and cited at the end of each chapter provide extensive coverage of all conditions discussed.

Some words for the editors of the monograph. For the first time in the 50-year history of the prestigious Monographs in Clinical Cytology, the same authors have been responsible for 2 different volumes of the series. Dr. Matias Jiménez-Ayala and Dr. Beatriz Jiménez-Ayala Portillo were also editors of volume 17, entitled Endometrial Adenocarcinoma: Prevention and Early Diagnosis. This fact reflects the extensive experience of both editors in the field of glandular lesions of the female genital tract. As mentioned before, in this book they invited the most prestigious cytopathologists around the world with experience in glandular lesions to write, ensuring the excellent quality of the text.

In summary, this monograph is once more a valuable addition to the Karger series Monographs in Clinical Cytology, which is edited by Dr. Svante Orell, and I am quite sure that this book will be a practical bench resource for all professionals involved in the cytological diagnosis of glandular lesions of the female genital tract.

Fernando Schmitt, MD, PhD, FIAC
General Secretary of the International Academy of Cytology
Institute of Pathology and Molecular Immunology of Porto University, IPATIMUP
Medical Faculty of Porto University, Porto
## List of Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACC</td>
<td>Adenoid cystic carcinoma</td>
</tr>
<tr>
<td>AD</td>
<td>Adenosis</td>
</tr>
<tr>
<td>ADSC</td>
<td>Adenosquamous carcinoma of the cervix</td>
</tr>
<tr>
<td>AEC</td>
<td>Atypical endocervical cells</td>
</tr>
<tr>
<td>AEmC</td>
<td>Atypical endometrial cells</td>
</tr>
<tr>
<td>AGC</td>
<td>Atypical glandular cells</td>
</tr>
<tr>
<td>AH</td>
<td>Atypical hyperplasia</td>
</tr>
<tr>
<td>AIS</td>
<td>Endocervical adenocarcinoma in situ</td>
</tr>
<tr>
<td>ASC-H</td>
<td>Atypical squamous cells, high-grade SIL not excluded</td>
</tr>
<tr>
<td>ASC-US</td>
<td>Atypical squamous cells of undetermined significance</td>
</tr>
<tr>
<td>ASR</td>
<td>Arias-Stella reaction</td>
</tr>
<tr>
<td>BGC</td>
<td>Bartholin gland carcinoma</td>
</tr>
<tr>
<td>BS</td>
<td>Bethesda System</td>
</tr>
<tr>
<td>CCA</td>
<td>Clear cell adenocarcinoma</td>
</tr>
<tr>
<td>CE</td>
<td>Cervical endometriosis</td>
</tr>
<tr>
<td>CGIN</td>
<td>Cervical glandular intraepithelial neoplasia</td>
</tr>
<tr>
<td>CIN</td>
<td>Cervical intraepithelial neoplasia</td>
</tr>
<tr>
<td>CIS</td>
<td>Squamous carcinoma in situ</td>
</tr>
<tr>
<td>CVS</td>
<td>Cervicovaginal smear</td>
</tr>
<tr>
<td>DES</td>
<td>Diethylstilbestrol</td>
</tr>
<tr>
<td>EA</td>
<td>Endocervical adenocarcinoma</td>
</tr>
<tr>
<td>EBT</td>
<td>Endometrial brushing techniques</td>
</tr>
<tr>
<td>EC</td>
<td>Endometrial cytology</td>
</tr>
<tr>
<td>EH</td>
<td>Endometrial hyperplasia</td>
</tr>
<tr>
<td>EIA</td>
<td>Early invasive adenocarcinoma</td>
</tr>
<tr>
<td>EIN</td>
<td>Endometrial intraepithelial neoplasia</td>
</tr>
<tr>
<td>EmA</td>
<td>Endometrial adenocarcinoma</td>
</tr>
<tr>
<td>EMBT</td>
<td>Endocervical mucinous borderline tumor</td>
</tr>
<tr>
<td>EN</td>
<td>Endometrioid neoplasia</td>
</tr>
<tr>
<td>EP</td>
<td>Endocervical polyp</td>
</tr>
<tr>
<td>FNAC</td>
<td>Fine needle aspiration cytology</td>
</tr>
<tr>
<td>FT</td>
<td>Fallopian tube</td>
</tr>
<tr>
<td>FTC</td>
<td>Fallopian tube carcinoma</td>
</tr>
<tr>
<td>GCC</td>
<td>Glassy cell carcinoma of cervix</td>
</tr>
<tr>
<td>GCT</td>
<td>Granulosa cell tumor</td>
</tr>
<tr>
<td>HC2</td>
<td>Hybrid Capture 2</td>
</tr>
<tr>
<td>HPV</td>
<td>Human papillomavirus</td>
</tr>
<tr>
<td>HSIL</td>
<td>High-grade squamous intraepithelial lesion</td>
</tr>
<tr>
<td>IMBT</td>
<td>Intestinal mucinous borderline tumor</td>
</tr>
<tr>
<td>IUD</td>
<td>Intrauterine device</td>
</tr>
<tr>
<td>LBP</td>
<td>Liquid-based preparation</td>
</tr>
<tr>
<td>LUS</td>
<td>Lower uterine segment</td>
</tr>
<tr>
<td>MA</td>
<td>Mucinous adenocarcinoma</td>
</tr>
<tr>
<td>MBT</td>
<td>Mucinous borderline tumor</td>
</tr>
<tr>
<td>MC</td>
<td>Metastatic carcinomas</td>
</tr>
<tr>
<td>MGH</td>
<td>Microglandular hyperplasia</td>
</tr>
<tr>
<td>MT</td>
<td>Metastases</td>
</tr>
<tr>
<td>NOS</td>
<td>Not otherwise specified</td>
</tr>
<tr>
<td>PB</td>
<td>Psammoma bodies</td>
</tr>
<tr>
<td>PD</td>
<td>Paget’s disease</td>
</tr>
<tr>
<td>PH</td>
<td>Papillary hidradenoma</td>
</tr>
<tr>
<td>PHGC</td>
<td>Post-hysterectomy glandular cells</td>
</tr>
<tr>
<td>RVF</td>
<td>Rectovaginal fistulae</td>
</tr>
<tr>
<td>SA</td>
<td>Serous adenocarcinoma</td>
</tr>
<tr>
<td>SBT</td>
<td>Serous borderline tumor</td>
</tr>
<tr>
<td>SCC</td>
<td>Squamous cell carcinoma</td>
</tr>
<tr>
<td>SIL</td>
<td>Squamous intraepithelial lesion</td>
</tr>
<tr>
<td>SPC</td>
<td>Serous papillary carcinoma</td>
</tr>
<tr>
<td>SSPC</td>
<td>Serous surface papillary carcinoma of the ovary</td>
</tr>
<tr>
<td>TM</td>
<td>Tubal metaplasia</td>
</tr>
<tr>
<td>VC</td>
<td>Vulvar carcinoma</td>
</tr>
<tr>
<td>VGA</td>
<td>Villoglandular adenocarcinoma</td>
</tr>
<tr>
<td>VIN</td>
<td>Vulvar intraepithelial neoplasia</td>
</tr>
<tr>
<td>VSIL</td>
<td>Vulvar squamous intraepithelial lesion</td>
</tr>
</tbody>
</table>
List of Authors

Francesc Alameda, MIAC. Department of Pathology, Hospital del Mar, Barcelona, Spain. Officer, Spanish Society of Cytology (Chapter 12).

Carmen Alvarez-Santín, MIAC. Former Professor of Pathology, University of Montevideo, Uruguay. Secretary General, Latin American Society of Cytology (Chapter 8).

Matías Jiménez-Ayala, FIAC. Instituto Jiménez-Ayala, Madrid. Former Chair, Department of Cytology, Hospital Universitario Gregorio Marañón, Madrid, Spain. Former President of the International Academy of Cytology (Chapters 5, 6, 7, 9, 10, 11).

Beatriz Jiménez-Ayala Portillo, MIAC. Director, Instituto Jiménez-Ayala, Madrid, Spain (Chapters 3, 5, 10, 11).

Belén Lloveras, Department of Pathology, Hospital del Mar, Barcelona, Spain (Chapter 12).

Dina R. Mody, MD. Professor of Pathology and Laboratory Medicine, Weill Medical College of Cornell University. Director of Cytology Laboratory and Fellowship Program, The Methodist Hospital, Houston, Tex., USA (Chapter 2).

Ritu Nayar, MIAC. Professor of Pathology and Director of Cytopathology, Northwestern University, Feinberg School of Medicine, Chicago, Ill., USA (Chapter 2).

Manuel Nevado Santos, MIAC. Chair, Department of Pathology, Hospital Infanta Cristina, Parla, Madrid, Spain (Chapter 1).

Lara Pijuán, Department of Pathology, Hospital del Mar, Barcelona, Spain (Chapter 12).

Fernando Pinedo Moraleda, Chair, Department of Pathology, Hospital Universitario Fundación Alcorcón, Madrid, Spain (Chapters 1, 9, 10).

Maria Carmen Rodríguez Alvarez. Chair, Dermatopathology Area, Department of Pathology, Centro Hospitalario Pereira Rosell, Montevideo, Uruguay (Chapter 9).

Volker Schneider, FIAC. Head, Pathology Laboratory, Freiburg, Germany. Former Secretary General, International Academy of Cytology (Chapter 4).

Adela Sica. Department of Pathology, University of Montevideo, Montevideo, Uruguay (Chapter 8).

Michael Thrall, Assistant Professor, Department of Pathology and Laboratory Medicine, Weill Medical College of Cornell University, The Methodist Hospital, Houston, Tex., USA (Chapter 2).