Encyclopedia of Pathology
Series Editor: J.H.J.M. van Krieken

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Philip T. Cagle
Keith M. Kerr *Editors*

Pulmonary Pathology

Neoplastic and Non-neoplastic

Springer

Encyclopedia of Pathology

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The scope of this 15–20-volume set encompasses the entire field of pathology ranging from general pathological terms to specific diseases to diagnostic methods. Published as print edition and online version (eReference) in the Springer Reference Program each topical volume sticks out by clearly and homogenously structured entries. A team of international experts guarantee that the essays and definitions are scientifically sound. The A-Z format of each topical volume allow readers to quickly and easily find the information they need. The major advantage of the encyclopedia is the way it makes relevant information available not only to pathologists, but also to all clinicians and researchers of the neighboring disciplines working together with pathologists who occasionally might wish to look up terms online.

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Philip T. Cagle • Keith M. Kerr
Editors

Pulmonary Pathology

Neoplastic and Non-neoplastic

With 410 Figures and 9 Tables

Springer

Editors
Philip T. Cagle
Department of Pathology and
Genomic Medicine
Houston Methodist Hospital
Houston, TX, USA

Keith M. Kerr
Department of Pathology
Aberdeen University Medical School
Aberdeen Royal Infirmary
Aberdeen, UK

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Series Preface

When Denis Diderot started the first encyclopedia in the eighteenth century, it was a groundbreaking and timely event. It was the time of the Enlightenment, and knowledge was seen as something which was to be spread to many and to build upon by creating new knowledge. His ambition was to bring all available knowledge together in one series of books so that every person who could read has access to all there is to know. Nowadays, in a time of easily accessible knowledge, the question is whether there is still need of an encyclopedia. It is obvious that the amount of knowledge is such that it is not possible to bring it all together in one encyclopedia. One may argue that the Internet is the encyclopedia of today, but that misses an important point of Diderot, a point that is probably even more valid today. He created a team that valued information and selected what was worth to be presented in the encyclopedia. He recognized that science is not a democratic process where the majority decides what is true and valuable, but rather a growing body of knowledge in which radical ideas from individuals may bring about huge changes, even though most would reject these new ideas in the beginning. Indeed, the Internet lacks such authority and it is not easy to select valuable information from nonsense, especially when one is not an expert in a certain field.

It is therefore that an encyclopedia is only as good as the team that creates it. It goes without saying the team that is responsible for the Encyclopedia of Pathology consists of recognized experts in the field. Pathology is a growing medical discipline in which the amount of information is probably already more than that the whole encyclopedia of Diderot contained. For experts in subspecialties within pathology, it is already almost impossible to keep an overview on new developments and to select relevant from less relevant new information. There are plenty of textbooks for every disease group, and scientific literature is available for most pathologists through PubMed or GoogleScholar. What is lacking is a systematic overview of what we know in an alphabetical order, easily accessible to all. The encyclopedia of pathology fills that gap. It is written by experts with the general pathologist in mind and also specialist from other disciplines. It will consist of a series of volumes on subspecialties, and when it is completed there will be an online version combining these. Yearly updates from the online version is foreseen and readers are welcome to provide suggestions for improvement. These will be judged by the editorial team in order to keep the encyclopedia authoritative yet using the expertise of many.

Finally, it is my hope that the encyclopedia will grow into a reliable body of knowledge in pathology, enabling communication through a common language, and that it will grow and adapt to new developments.

Nijmegen, The Netherlands J. H. J. M. van Krieken
January 2018

Volume Preface

Pulmonary Pathology is a complex field that many pathologists find challenging due to the distinctive histology and tissue responses of the lungs. As a volume in *Springer's Encyclopedia of Pathology*, this book, *Encyclopedia of Pathology: Pulmonary Pathology (Non-neoplastic/Neoplastic)*, encompasses the numerous entities encountered in neoplastic and non-neoplastic lung disease for general pathologists, academic scholars and researchers, medical students and trainees, as well as practitioners of other medical disciplines whose pursuits intersect with pulmonary pathology. With its homogeneously structured entries arranged in alphabetical order, it offers rapid access to efficiently organized information and an accompanying online version with links for definitions and shared entries that is intended to expedite comprehension of this frequently difficult discipline.

To compile such an extensive compendium of encyclopedia entries, diverse scholars from multiple nations were required to invest their time, energy, and expertise. A special gratitude is owed to these many individuals, too numerous to list separately here, who contributed the authoritative essays and valuable illustrations that make up this volume. In addition, the volume would not have been possible without the excellent team of industrious editors and staff at Springer, who individually span both time and functions during the creation of this book, and the impressive leadership of Series Editor Professor Han van Krieken who toiled extensively to supervise the completion of the *Encyclopedia*.

This volume is expected to be a versatile implement for those requiring ready accessibility to information on pulmonary pathology. As a component of *Springer's Encyclopedia of Pathology*, it is our hope that pathologists and other medical specialists will find *Encyclopedia of Pathology: Pulmonary Pathology (Non-neoplastic/Neoplastic)* to be a valuable tool in their everyday practice, medical students and trainees will find it a beneficial resource in their studies, and researchers will find it a utilitarian asset in their investigations.

Houston, USA — Philip T. Cagle, M.D.
Aberdeen, UK — Keith M. Kerr, M.D.

Acknowledgments

We would like to acknowledge the industrious team at Springer who assisted us with this endeavor

Editor Biography

Philip T. Cagle, M.D., is the Editor-in-Chief of the *Archives of Pathology and Laboratory Medicine*, Director of Pulmonary Pathology at Houston Methodist Hospital, Professor of Pathology and Laboratory Medicine at Weill Cornell Medical College, and Executive Advisor of the Pulmonary Pathology Society. Dr. Cagle received his M.D. degree from the University of Tennessee College of Medicine in Memphis in 1981. After completing his pathology residency at the Baylor College of Medicine in Houston, Texas, from 1981 to 1985, he completed a fellowship in pulmonary pathology at the University of British Columbia in Vancouver, Canada, from 1985 to 1987. In 1987, he joined the faculty at Baylor College of Medicine and joined the faculty at Houston Methodist Hospital and Weill Cornell Medical College in 2004. Dr. Cagle is Co-chair and co-author of the College of American Pathologists (CAP)/International Association for the Study of Lung Cancer/Association for Molecular Pathology Guidelines for Lung Cancer Predictive Biomarker Testing, Chair of the CAP Cancer Biomarker Reporting Committee, and Advisor to several other CAP Committees. He is current Program Committee Chair and former President of the Pulmonary Pathology Society as well as Education Council Chair for the Texas Society of Pathologists. He is editor of 20 textbooks on pulmonary pathology, editor of 2 electronic books, series editor for 3 book series, and author of over 100 book chapters and over 200 journal articles. Dr. Cagle is a popular speaker nationally and internationally including nearly 100 lectures and courses outside the United States. Dr. Cagle is a recipient of 75 professional awards including the Houston Society of Clinical Pathologists Harlan J. Spjut Award (2008), CAP

Distinguished Patient Care Award (2013), the CAP Pathologist of the Year Award (2013), the Alfred Soffer Research Award from the American College of Chest Physicians (first recipient-1992), the Texas Society of Pathologists John J. Andujar M.D. Citation of Merit Award (2014), the Chinese American Pathology Association, Honorary Award (first recipient-2016), and America's Most Honored (Top 1%) Professionals Award (2016, 2017).

Keith M. Kerr has been a Consultant Pathologist in Aberdeen since 1989. He was awarded an Honorary Chair in Pulmonary Pathology by the University of Aberdeen in 2006.

Throughout his career, he has worked in diagnostic histopathology with a special interest in thoracic pathology, while keeping close links with the clinical practice of thoracic medicine, especially thoracic oncology. He has an active research interest in his own laboratory and through national and international collaboration. He has been a member of IASLC for over 20 years and is a member of the IASLC Pathology Panel. He was elected to the IASLC Board of Directors for 4 years, 2013–2017. In 2017, he received the IASLC Mary Matthews Award for Pathology and Translational Research. He is a member of ESMO and serves on the ESMO Lung Educational Faculty. He is Pathology Chair for the ETOP Lungscape group. He served on the international Pulmonary Pathology Society council. He was a member of the panel for the 2004 and 2015 WHO lung cancer classifications. He has worked on numerous clinical research lung cancer trials groups, guideline development for lung cancer and mesothelioma diagnosis and management, and conference scientific committees. He is a panel member for the revision of the CAP/IASLC/AMP guidelines for molecular pathology testing in lung cancer. He is an Associate Editor for the *Journal of Thoracic Oncology.*

Series Editor Biography

J. H. J. M. van Krieken is a pathologist with special expertise in the fields of hematopathology and the pathology of the gastrointestinal tract. He was Professor for tumor pathology since 1999 and kept from 2005 to 2015 the Chair of pathology at the Radboud University Nijmegen Medical Centre in Nijmegen. He furthermore served as Chairman of the Board of the Oncology Institute of the Radboud University, Nijmegen, from 2008 to 2016. Since 2016, he is the Rector Magnificus (Vice Chancellor) of the Radboud University.

He was the Treasurer/Secretary of the European Association for Hematopathology from 2000 to 2008, from 2003 to 2011 the Treasurer, from 2013 to 2015 the President of the European Society for Pathology (ESP), and from 2015 to 2017 the past-President of the ESP. Furthermore, he coordinates the ESP quality assessment program and is the Chair of IQN Path. He is (co) author of more than 500 papers in peer-reviewed journals (H-index 82), has written chapters in books on pathology and oncology, is editor of a Dutch textbook on oncology, and serves on the editorial board of the *American Journal of Surgical Pathology*, was managing editor of *Virchows Archiv* from 2013 to 2017, and was the chief editor of the *Journal of Hematopathology* from 2008 to 2018. Since 2011, he is member of the German Academy of Sciences Leopoldina, and since 2014 of Academia Europea and Honorary Fellow of the Royal Society of Pathology of Great Britain and Ireland.

Contributors

Marie Christine Aubry Department of Pathology, Mayo Clinic, Rochester, MN, USA

Roberto Barrios Department of Pathology, The Methodist Hospital, Houston, TX, USA

Ghada Bashat Department of Pathology, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK

Mary Beth Beasley Department of Pathology, Mount Sinai Medical Center, New York, NY, USA

Adam Beattie Department of Pathology, Northwestern University, Chicago, IL, USA

Jennifer M. Boland Department of Pathology, Mayo Clinic, Rochester, MN, USA

Alain Borczuk Department of Pathology, The Methodist Hospital, Houston, TX, USA

Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY, USA

Philip T. Cagle Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, TX, USA

Anne Patricia Campbell Cellular Pathology, Hull and East Yorkshire Hospitals NHS Trust, Hull, UK

Paul Cane Department of Histopathology, Guy's and St Thomas' NHS Foundation Trust St Thomas' Hospital, London, UK

Lina Carvalho Faculty of Medicine, Institute of Anatomical and Molecular Pathology, Coimbra, Portugal

Alberto Cavazza Unità Operativa di Anatomia Patologica, Arcispedale Santa Maria Nuova-IRCCS, Reggio Emilia, Italy

Charles Chalfant Department of Biochemistry and Molecular Biology, Virginia Commonwealth University, Richmond, VA, USA

Research Career Scientist, Research and Development, Hunter Holmes McGuire VAMC, Richmond, VA, USA

Andrea D. Chapman Department of Pathology, Aberdeen University Medical School, Aberdeen Royal Infirmary, Aberdeen, UK

Lucian R. Chirieac Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Belinda E. Clarke Pathology Queensland, The Prince Charles Hospital, Chermside, QLD, Australia

Caroline Laura Coghlin Department of Pathology, Aberdeen Royal Infirmary, Aberdeen, UK

Wendy Cooper Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Camperdown, NSW, Australia

Sydney Medical School, University of Sydney, Sydney, NSW, Australia

School of Medicine, University of Western Sydney, South Penrith, NSW, Australia

Suzanne Crumley Department of Pathology, The Methodist Hospital, Houston, TX, USA

Sanja Dacic Department of Pathology, University of Pittsburgh Medical Center, Presbyterian University Hospital, Pittsburgh, PA, USA

Moira Davie Department of Pathology, Aberdeen Royal Infirmary Aberdeen University Medical School, Aberdeen, UK

Michael A. den Bakker Department of Pathology, Maasstad Hospital and Erasmus MC, Rotterdam, The Netherlands

Craig P. C. Dick Department of Pathology, Southern General Hospital, Glasgow, UK

Mukul K. Divatia Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, TX, USA

Rachel Donohue Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, TX, USA

Edwina E. Duhig The John Flynn Hospital, Sullivan Nicolaides Pathology, Tugun, QLD, Australia

Sinclair R. Dundas Pathology Department, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK

Alessandra Fabbri Department of Pathology and Laboratory Medicine, Fondazione IRCCS National Cancer Institute and University of Milan School of Medicine, Milan, Italy

Department of Oncology and Hemato-Oncology, Università degli Studi of Milan, Milan, Italy

Michael C. Fishbein Department of Pathology and Laboratory Medicine, UCLA Center for the Health Sciences, Los Angeles, CA, USA

Armando E. Fraire Department of Pathology, University of Massachusetts Memorial Medical Center, Worcester, MA, USA

Teri J. Franks The Joint Pathology Center, Silver Spring, MD, USA

Javier Gómez Román Servicio de Anatomía Patológica. Hospital Universitario Marqués de Valdecilla, Servicio Cántabro de Salud. Universidad de Cantabria. IDIVAL, Santander, Cantabria, Spain

Anthony A. Gal Department of Pathology, Emory University Hospital, Atlanta, GA, USA

Mary Louise Galloway Department of Pathology, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK

Jeffrey R. Galvin University of Maryland School of Medicine, Baltimore, MD, USA

American Institute for Radiologic Pathology, Silver Spring, MD, USA

Yimin Ge Department of Pathology, Houston Methodist Hospital, Weil Medical College of Cornell University, Houston, TX, USA

Natalia Golardi Department of Pathology, The Methodist Hospital, Houston, TX, USA

Blythe K. Gorman Department of Pathology, Physician Organization – Pathology, The Methodist Hospital, Houston, TX, USA

John R. Gosney Department of Pathology, Royal Liverpool University Hospital, Liverpool, UK

Anna Catherine Green Department of Histopathology, Guy's and St Thomas' NHS Foundation Trust St Thomas' Hospital, London, UK

Ulrike Gruber-Moesenbacher Institute of Pathology, University Teaching Hospital, Feldkirch, Austria

Frederick Peter Guengerich Department of Biochemistry and Center in Molecular Toxicology, Vanderbilt University School of Medicine, Nashville, TN, USA

Donald Guinee Jr. Department of Pathology, Virginia Mason Medical Center, Seattle, WA, USA

Susan L. Haley Department of Pathology, Houston Methodist Hospital, Houston, TX, USA

Abida K. Haque Department of Pathology, The Methodist Hospital, Houston, TX, USA

Justin C. Hardin Department of Pathology, The Methodist Hospital, Weill Cornell College of Medicine, Houston, TX, USA

Aaron M. Harvey Department of Pathology, The Methodist Hospital, Houston, TX, USA

Michelle C. Hure Department of Pathology, University of Massachusetts Memorial Medical Center, Worcester, MA, USA

Aliya N. Husain Department of Pathology, University of Chicago, Chicago, IL, USA

Jaishree Jagirdar Department of Pathology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Peter W. Johnston Department of Pathology, Aberdeen Royal Infirmary, NHS Grampian, Aberdeen, UK

Jeffrey L. Jorgensen Department of Hematopathology, The University of Texas – MD Anderson Cancer Center, Houston, TX, USA

Douglas A. Julin Department of Chemistry and Biochemistry, University of Maryland, College Park, MD, USA

Izidor Kern University Clinic Golnik, Golnik, Slovenia

Keith M. Kerr Department of Pathology, Aberdeen University Medical School, Aberdeen Royal Infirmary, Aberdeen, UK

Kelly Khan Physician Organization - Pathology, The Methodist Hospital, Houston, TX, USA

Andras Khoor Department of Pathology, Mayo Clinic, Jacksonville, FL, USA

Sonja Klebe Department of Anatomical Pathology, Flinders University and SA Pathology at Flinders Medical Centre, Adelaide, SA, Australia

Jason Koshy Pathology Education, University of Texas Medical Branch, Galveston, TX, USA

Rashmi Lahiri Department of Pathology, Aberdeen Royal Infirmary, Aberdeen, UK

Gavin M. Laing Department of Pathology, Aberdeen University Medical School, Aberdeen Royal Infirmary, Aberdeen, UK

Nathan Lee Department of Pathology, The Methodist Hospital, Houston, TX, USA

Kevin Orr Leslie Department of Laboratory Medicine and Pathology, Mayo Clinic, Scottsdale, AZ, USA

X. William Li Department of Pathology, The Methodist Hospital, Houston, TX, USA

Leslie Litzky Department of Pathology, University of Pennsylvania Medical Center, Philadelphia, PA, USA

Peh Sun Loo Department of Pathology, Aberdeen Royal Infirmary, Aberdeen, UK

Alberto M. Marchevsky Department of Anatomic Pathology, Cedars Sinai Medical Center, Los Angeles, CA, USA

Elizabeth McQuitty The University of Texas Medical Branch, Houston, TX, USA

Ross A. Miller Department of Pathology and Genomic Medicine, Houston Methodist, Houston Methodist Institute of Academic Medicine, Houston, TX, USA

Tara N. Miller Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, TX, USA

Mari Mino-Kenudson Department of Pathology, Massachusetts General Hospital, Boston, MA, USA

M. Kamran Mirza Department of Pathology, University of Chicago, Chicago, IL, USA

Hannah Monaghan Department of Histopathology, Royal Infirmary Edinburgh, Edinburgh, Midlothian, Scotland, UK

M. Angeles Montero-Fernandez Department of Pathology, Val d'Hebron University Hospital, Barcelona, Spain

Sanjay Mukhopadhyay Department of Pathology, State University of New York Upstate Medical University, Syracuse, NY, USA

Nicole Nelles Department of Pathology and Genomic Medicine, Houston Methodist, Houston, TX, USA

Angheliki Nomikos Pathology Department, Aberdeen Royal Infirmary, Aberdeen, Scotland, UK

Jacqueline O'Hare Department of Pathology, The Methodist Hospital, Houston, TX, USA

Paavo Pääkkö Department of Pathology, Oulu University Hospital, Oulu, Finland

Mauro Giulio Papotti Department of Clinical and Biological Sciences, University of Turin at San Luigi Hospital, Orbassano, Torino, Italy

Department of Oncology, University of Turin at San Luigi Hospital, Orbassano, Torino, Italy

Margaret A. Park Department of Biochemistry and Molecular Biology, Virginia Commonwealth University, Richmond, VA, USA

Adam R. Parks Molecular Control and Genetics Section, Gene Regulation and Chromosome Biology Laboratory, National Cancer Institute, National Institutes of Health, Frederick, MD, USA

Giuseppe Pelosi Department of Pathology and Laboratory Medicine, Fondazione IRCCS National Cancer Institute and University of Milan School of Medicine, Milan, Italy

Department of Oncology and Hemato-Oncology, Università degli Studi of Milan, Milan, Italy

Joseph E. Peters Department of Microbiology, Cornell University, Ithaca, NY, USA

Jo Elle Peterson Department of Pathology, The Methodist Hospital, Houston, TX, USA

Gabriela M. Quiroga-Garza Department of Pathology, The Methodist Hospital, Houston, TX, USA

Kirtee Raparia Department of Pathology, Northwestern University Feinberg, Chicago, IL, USA

Doris M. Rassl Papworth Hospital, Cambridgeshire, UK

Fiona S. Robertson Department of Pathology, Aberdeen Royal Infirmary, Aberdeen, UK

Anja C. Roden Mayo Clinic Rochester, Rochester, MN, USA

Oscar Roncal The University of Texas Medical Branch, Galveston, TX, USA

Jenny Ross Department of Pathology, University of Texas Health Science Center at San Antonio, San Antonio, TX, USA

Giulio Rossi Operative Unit of Pathologic Anatomy, Azienda Arcispedale S. Maria Nuova/IRCCS, Reggio Emilia, Italy

Prudence A. Russell St Vincent's Hospital, Melbourne, VIC, Australia

Donald M. Salter Centre for Genomics and Experimental Medicine, MRC IGMM, University of Edinburgh, Western General Hospital, Edinburgh, Scotland, UK

Frank Schneider Department of Pathology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

Vijay Sharma Department of Pathology, Aberdeen Royal Infirmary and the University of Aberdeen, Aberdeen, Scotland, UK

Lynette M. Sholl Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Gabriel Sica Department of Pathology, Emory University, Atlanta, GA, USA

Birgit Guldhammer Skov Department of Pathology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark

Angelica Sonzogni Department of Pathology and Laboratory Medicine, Fondazione IRCCS National Cancer Institute and University of Milan School of Medicine, Milan, Italy

Department of Oncology and Hemato-Oncology, Università degli Studi of Milan, Milan, Italy

Albert Su Department of Pathology and Laboratory Medicine, UCLA Center for the Health Sciences, Los Angeles, CA, USA

Hidehiro Takei Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Weill Medical College of Cornell University, Houston, TX, USA

Michael J. Thrall Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, TX, USA

Erik Thunnissen Department of Pathology, VU University Medical Center, Amsterdam, The Netherlands

Wim Timens Department of Pathology and Medical Biology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

Joseph F. Tomashefski Jr. Department of Pathology, MetroHealth Medical Center, Cleveland, OH, USA

Simon Trotter Department of Cellular Pathology, Birmingham Heartlands Hospital, Birmingham, UK

William A. H. Wallace Deparment of Pathology, Royal Infirmary of Edinburgh, Edinburgh, UK

Arne Warth Institute of Pathology, University Hospital Heidelberg, Heidelberg, Germany

Daniel B. Wimmer Department of Pathology, The Methodist Hospital, Houston, TX, USA

Jana Wimmer Department of Pathology, The Methodist Hospital, Houston, TX, USA

Angela M. Wright Department of Pathology and Genomic Medicine, Houston Methodist Hospital, Houston, TX, USA

Anjana Yeldandi Department of Pathology, Northwestern University, Chicago, IL, USA

Eunhee S. Yi Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine, Rochester, MN, USA

Jun Zhang Mayo Medical School, Mayo Clinic, Rochester, MN, USA

A

Acinic Cell Tumor, Lung

Caroline Laura Coghlin[1] and Keith M. Kerr[2]
[1]Department of Pathology, Aberdeen Royal Infirmary, Aberdeen, UK
[2]Department of Pathology, Aberdeen University Medical School, Aberdeen Royal Infirmary, Aberdeen, UK

Synonyms

Acinic cell carcinoma; Acinic cell type; Pulmonary salivary gland tumor

Definition

Originally described by Fechner and his colleagues in 1972, pulmonary acinic cell carcinoma ("Fechner tumor") is a rare, low grade, malignant epithelial tumor with cytological differentiation toward serous acinar cells. The tumor shows homology to its more common salivary gland counterpart and is thought to originate from pluripotent cells within the submucosal glands of the bronchi and the trachea. Acinic cell carcinoma has been described in many other sites other than the lung and the salivary glands, including the breast, upper respiratory tract, and within ectopic salivary gland foci in lymph nodes. Salivary gland-type tumors of the lung are rare with adenoid cystic carcinoma and mucoepidermoid carcinoma accounting for most previously reported cases. Most reported cases of pulmonary acinic cell carcinoma have been discovered as incidental findings on imaging although those growing in an endobronchial location may present with persistent cough and obstructive symptoms.

Clinical Features

- **Incidence**
  This is a very rare tumor with only 19 cases described in the literature to date.
- **Age**
  Acinic cell carcinoma of the lung is more common in adults but has been described in a 12-year-old and in a 4-year-old child (in the latter, as a polypoid endobronchial mass causing obstruction). The age range is 4–75 years, with a mean age of 45 years.
- **Sex**
  There is a male to female ratio of 5:4.
- **Site**
  The tumor usually arises as a parenchymal nodule or, more rarely, as an endobronchial mass (which may cause obstruction). It is vitally important to exclude acinic cell carcinomas at other sites (notably the salivary glands) in order to exclude the possibility of a metastasis. Three of the five cases of pulmonary acinic cell carcinoma described by Moran et al. were located in the right middle lobe,

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while one was located in the left upper lobe and one in the right upper lobe. Macroscopically, three of these cases were subpleural nodules, one was a well-circumscribed parenchymal mass and one was an endobronchial submucosal tumor.

- **Treatment**
  The treatment of choice is complete surgical excision. Lobectomy is the operation most commonly employed for the resection of salivary gland-type lung tumors.
- **Outcome**
  Acinic cell carcinoma of the lung is an indolent tumor with a generally good prognosis (Ukoha et al.). Surgical excision is usually curative, but two cases have been described which showed lymph node metastases. In one of the latter cases, the tumor recurred 20 months later (Lee et al.).

  Although some attempt has been made to grade acinic cell carcinomas at other sites (the salivary glands) using histological features, it is believed that prognosis in lung tumors is more strongly linked to degree of local invasiveness and completeness of surgical excision. In salivary gland tumors, only overt dedifferentiation is consistently associated with more aggressive behavior. Microscopic features which have previously been considered as markers of aggressive biological behavior include pleomorphism, necrosis, increased mitotic activity, and perineural invasion. Perhaps importantly, the only recorded case of recurrent acinic cell carcinoma of the lung showed perineural invasion in the original resection specimen (Lee et al.).

Macroscopy

Pulmonary acinic cell carcinomas are usually circumscribed but lack well-defined capsules. They vary in size from 1 to 5 cm. Occasionally, the tumors present as polypoid endobronchial growths. They have a brownish-white to yellow homogeneous cut surface that lacks zones of necrosis or hemorrhage.

Microscopy

Histologically, acinic cell carcinomas of the lung resemble their more common salivary gland counterparts. Differentiation toward serous-type acinar cells is observed although ductal and myoepithelial differentiation may also occur, in keeping with their postulated origin from pluripotent reserve/stem cells of the tracheobronchial tree. The architecture is variable with acinar, tubulo-papillary, sheet-like, or nested growth patterns described. The constituent cells are uniform and polygonal with abundant granular amphophilic or clear cytoplasm. The nuclei are generally small and round to oval with small, indistinct nucleoli. Mitotic figures are infrequent with an average count of 1/50 high-power fields. Pleomorphism, necrosis, and an increased mitotic rate are lacking from typical cases of pulmonary acinic cell carcinoma. Nests and acinar units are surrounded by delicate fibrous septa. An organoid pattern of growth in acinic cell carcinomas occasionally mimics the appearance of a neuroendocrine tumor.

Characteristic periodic acid-Schiff (PAS) positive, diastase-resistant cytoplasmic granules are often found in the cells of acinic cell carcinoma although cases have been described in which this feature is focal or absent. Of the five cases described by Moran et al., only one was strongly PAS positive and two showed weak, patchy positivity (Moran et al.). Mucin stains are negative. In one case presenting as an endobronchial lesion in a child, laminated, concentric psammoma-like bodies were found in acinar structures and in the fibrous stroma (Sabaratnam et al.).

Electron microscopy in acinic cell carcinoma reveals the presence of cytoplasmic 600–800 nm membrane-bound zymogen granules characteristic of serous acinar cells.

Immunophenotype

Immunohistochemical stains have a limited role in the diagnosis of acinic cell carcinoma. EMA and cytokeratin stains are positive, as would be expected in a tumor showing serous acinar

differentiation. Staining for amylase and alpha-1 chymotrypsin is variable and may be weak. Neuroendocrine markers such as chromogranin and synaptophysin are negative. S100 and vimentin are negative in acinic cell carcinoma.

Molecular Features

Molecular features of pulmonary acinic cell carcinoma are not yet described in the literature.

Differential Diagnosis

The differential diagnosis of acinic cell carcinoma of the lung includes several different lesions which show similar sheet-like or acinar architectural features and which are composed of cells with clear or granular cytoplasm. Metastatic acinic cell carcinoma should always be considered and excluded clinically especially as acinic cell carcinoma of the salivary glands can recur and metastasise many years after definitive treatment. Carcinoid tumors can have similar morphological features but show positivity for neuroendocrine markers such as synaptophysin and chromogranin. These are typically not expressed in acinic cell carcinomas although a single case of combined acinic cell carcinoma and carcinoid tumor of the lung has been described (Rodriguez et al.). Bronchial granular cell tumor can be excluded on the basis of its positivity for S100. Bronchial oncocytoma lacks the PAS positive, diastase-resistant granules observed in acinic cell carcinoma and shows numerous mitochondria on electron microscopy, rather than membrane-bound zymogen granules.

Clear cell tumors to be considered in the differential diagnosis include sugar tumor of the lung. This lesion is HMB45 positive and negative for cytokeratins. Primary clear cell carcinoma of the lung and metastatic renal cell carcinoma are largely differentiated from acinic cell carcinoma on the basis of morphological features. The former two malignancies show greater cytological atypia, more advanced invasiveness, and higher mitotic rates and areas of necrosis. Renal cell carcinoma contains both lipid and glycogen. The glycogen digests with diastase in contrast to the PAS positive, diastase-resistant granules often seen in acinic cell carcinoma.

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Acute Fibrinous and Organizing Pneumonia

Michael J. Thrall
Department of Pathology and Genomic Medicine,
Houston Methodist Hospital,
Houston, TX, USA

Synonyms

AFOP

Definition

Acute fibrinous and organizing pneumonia (AFOP) is an unusual histologic pattern of injury characterized by a combination of intra-alveolar "fibrin balls" and proliferation of young fibroblasts. The pattern is not specific for an

underlying entity. AFOP may be idiopathic or a presentation of infection, collagen vascular disease, environmental exposures, drug reactions, or other sources of acute lung injury. The absence of characteristics diagnostic of other entities including diffuse alveolar damage, eosinophilic pneumonia, and granulomatous inflammation is necessary to render the diagnosis.

Patients with AFOP may have two different presentations: acute and subacute. In the acute setting the patients develop a rapid-onset respiratory failure that leads to ventilator dependence and has a high mortality rate. The subacute presentation develops more slowly and causes a lesser degree of respiratory distress. Patients who do not need ventilator support generally recover and respond to treatment including steroids. About half of the patients fall into each of these categories. On computed tomography imaging AFOP may have a number of different and nonspecific appearances ranging from diffuse bilateral infiltrates to a localized nodule. Therefore, the diagnosis depends entirely on histologic examination.

Since the entity of AFOP was first proposed, it has been considered most likely to be a morphologic variant of diffuse alveolar damage that lacks the hyaline membranes characteristic of that entity. The frequently aggressive clinical course observed in these patients provides additional support for this hypothesis. However, few cases have been reported in the literature since the initial description of the entity, and no additional series have been published to provide more insight into the pathogenesis or natural history of this disease.

Clinical Features

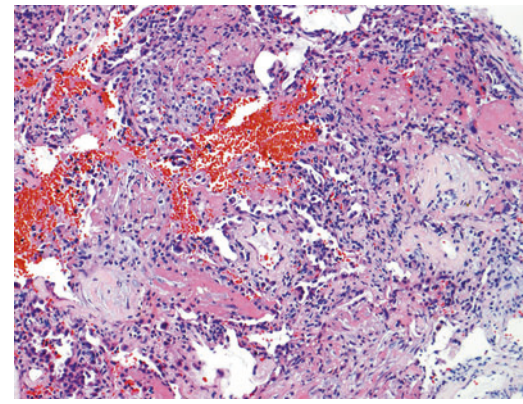
- **Incidence**
  No incidence studies have been performed for AFOP, but the diagnosis is considered very rare.
- **Age**
  Based on the small number of available reports, AFOP appears to be a disease of middle-aged and elderly adults.
- **Sex**
  No definite sex predilection has been found for this entity.
- **Site**
  AFOP only affects the lungs, though it may be associated with systemic illnesses.
- **Treatment**
  Treatment depends on patient symptoms. Acute cases frequently require mechanical ventilation and intensive care. Subacute cases require symptomatic treatment and may respond to steroids.
- **Outcome**
  Outcome depends primarily on clinical presentation. Patients with acute disease frequently progress to a fatal outcome, whereas subacute disease usually resolves.

Macroscopy

No published descriptions of the gross pathologic findings in AFOP are available.

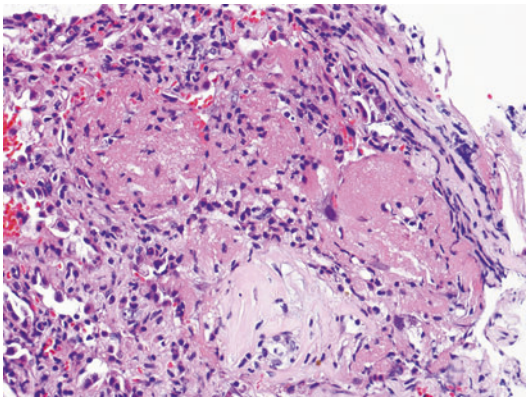
Microscopy

AFOP is defined by the histologic pattern of intra-alveolar "fibrin balls" combined with fibroblast proliferation (Fig. 1). The "fibrin balls" are

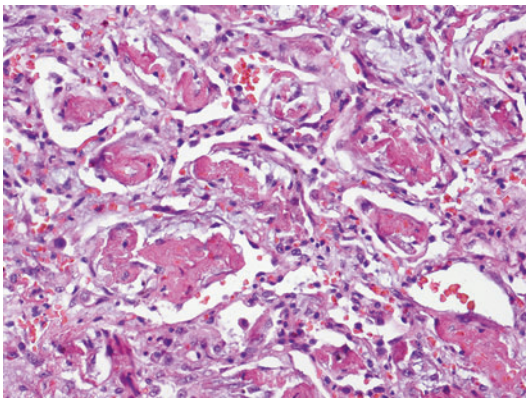


Acute Fibrinous and Organizing Pneumonia, Fig. 1 This low-power H&E stained view of AFOP in a transbronchial biopsy shows the patchy nature of the disease with aggregates of "fibrin balls" and fibroblast proliferation divided by an area of relatively preserved alveolated parenchyma with type II pneumocyte hyperplasia

rounded collections of fibrinous debris filling the alveolar space. The associated fibroblast proliferation may manifest as nearby Masson bodies of the type seen in organizing pneumonia (Fig. 2) or as organization of the fibrin balls with fibroblasts encircling the debris (Fig. 3). Trichrome staining highlights the fibroblastic element. Generally speaking the fibroblastic component is less prominent than the fibrin aggregates.



Acute Fibrinous and Organizing Pneumonia, Fig. 2 This higher-power view of the same H&E stained section shows how the fibrinous aggregates fill the alveolar spaces, forming round "balls." There is also a classic Masson body nearby, produced by young fibroblasts proliferating into an alveolar space



Acute Fibrinous and Organizing Pneumonia, Fig. 3 This high-power H&E stained view of AFOP in a wedge biopsy specimen demonstrates another pattern of fibroblast proliferation. Here the fibroblasts are seen surrounding some of the "fibrin balls" within alveolar spaces

Unlike diffuse alveolar damage, AFOP is usually a patchy process. Areas of involvement alternate with relatively spared areas of normal or near-normal parenchyma. Alveoli in or near the involved areas often show type II pneumocyte hyperplasia, and there is often an associated mild chronic inflammatory infiltrate. Rare neutrophils or eosinophils may be seen. Interstitial and alveolar edema is common. A minor component of interstitial myxoid change may be found. AFOP should not be diagnosed if the findings are focally present in the context of another predominant histologic pattern such as diffuse alveolar damage, organizing pneumonia, eosinophilic pneumonia, acute pneumonia, or granulomatous disease.

Immunophenotype

Immunohistochemistry has no known role in the diagnosis of AFOP.

Molecular Features

The molecular underpinnings of AFOP have not been investigated.

Differential Diagnosis

The primary differential diagnoses include diffuse alveolar damage, organizing pneumonia, and eosinophilic pneumonia. A diagnosis of AFOP should not be rendered if the histologic pattern fits one of these better-characterized entities.

References and Further Reading

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Acute Interstitial Pneumonia

Lynette M. Sholl and Lucian R. Chirieac
Department of Pathology, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA

Synonyms

Hamman-Rich disease

Definition

Acute interstitial pneumonia (AIP) is an idiopathic interstitial pneumonia characterized by abrupt disease onset and rapid progression leading to respiratory failure. It was originally described in the 1930s by Hamman and Rich as a fulminant diffuse interstitial fibrosis (Hamman and Rich 1935). Characteristically, patients are previously healthy adults that present following a 7–14-day prodromal upper respiratory tract illness. There is no association with smoking history. On chest X-ray, patients with AIP have diffuse bilateral pulmonary infiltrates; however higher-resolution computed tomography scans reveal the infiltrates to be patchy and more prominent in the dependent portions of the lungs. Pathologically, the features are indistinguishable from those of acute respiratory distress syndrome (ARDS)/**diffuse alveolar damage** (DAD). The etiology of AIP is unknown; however, the major pathway of lung injury is thought to be mediated by neutrophils via release of proteases and reactive oxygen species, leading to epithelial cell and basement membrane injury.

Clinical Features

- **Incidence**
  This is rare. The true incidence is unknown. Most published case series fail to distinguish between those cases that have an underlying trigger and those that are truly idiopathic.
- **Age**
  The mean age of involvement by AIP is 50–55 years, although a wide age range is reported, including in pediatric patients.
- **Sex**
  There is no sex predilection.
- **Site**
  AIP is characterized by diffuse bilateral lung involvement.
- **Treatment**
  There is no proven treatment for AIP. Glucocorticoids provide no clear benefit. Supportive care is the mainstay of treatment, frequently including mechanical ventilation.
- **Outcome**
  The mortality rate is greater than 50%, with most deaths occurring within 6 months of disease onset. Many survivors regain their baseline lung function or have only mild functional deficits; however a subset of patients suffers recurrent episodes of AIP, and some develop chronic interstitial lung disease. There are no known clinical or pathologic features that predict long-term outcomes.

Macroscopy

The lungs grossly appear firm and dusky, with a cut surface that appears diffusely gray and glistening, reflecting increased matrix deposition. Submillimeter cysts may be apparent, corresponding to alveolar duct dilatation. The lungs that progress to chronic fibrotic disease may acquire a cobblestone appearance, with alternating microcystic change and patchy scarring on the cut surface.