CURRENT UPDATES ON PATHOLOGY OF LUNG TUMORS

06 MAY 2013
MARRIOTT HOTEL • RIYADH, SAUDI ARABIA

PROGRAM

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Dear Colleagues,

I welcome you to the Current Update on the Pathology of Lung Tumors (CUPLT) organized by the Saudi Lung Cancer Group (SLCG), held at the Riyadh Marriott on 06 May 2013.

Saudi Lung Cancer Group (SLCG) is a multidisciplinary group under the umbrella of Saudi Thoracic Society (STS). The group’s mission to collaborate and lead national and international initiatives in lung cancer control including prevention, education, research and promotion of evidence-based practice, with a vision to become a regional leader and global participant in the fight against lung cancer and contributor to the advancement of knowledge in the field.

I would like to extend a great appreciation to our partners the pharmaceutical Industry for their continuing support to the Saudi Lung Cancer Group (SLCG) in general and to this event in particular.

We hope that CUPLT will meet your expectations and more.

Thank you for your participation and we hope to see you in our future activities.

Prof. Fouad Al Dayel, MD, FRCPA, FRCPath
Chairman, Department of Pathology and Laboratory Medicine
King Faisal Specialist Hospital & Research Centre
Riyadh, Saudi Arabia

Dear Colleagues,

On behalf of the Saudi Lung Cancer Group (SLCG), it gives me great pleasure to welcome you to the workshop and to the City of Riyadh.

The title of this workshop “Current Updates on Pathology of Lung Tumors” was selected to reflect the rapid changes and advancements that are taking place in lung tumor pathology. This is important because these changes, like digital revolution, advances in molecular genetics and demands on subspecialization in pathology, may represent challenges to pathologists. It is our responsibility as SLCG to provide our colleagues with all the resources to be prepared for these changes.

Another challenge is our limited ability to keep up with the vast information available everyday. Our need to enhance our knowledge and experience through training and education programs is increasing. We are required to manage the small lung biopsies to effectively provide diagnostic, prognostic and predictive information.

We do hope that attendance to this workshop will be a fulfilling experience and give you the opportunity to meet and interact with world and local authorities the field of lung pathology.

Prof. Fouad Al Dayel, MD, FRCPA, FRCPath
Chairman, Department of Pathology and Laboratory Medicine
King Faisal Specialist Hospital & Research Centre
Riyadh, Saudi Arabia
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EDUCATION
Amherst High School, Amherst, Massachusetts 1962-1965
Eagle Scout - 1962
Tulane University, New Orleans, Louisiana 1965-1967
Stanford University, Stanford, California 1967-1970
BA, cum laude (1969); Graduate Student at Large (1969-1970); NCAA Division IA Track and Field All-American (1968)
University of Michigan Medical School, Ann Arbor, Michigan 1970-1974
M.D., cum laude, Alpha Omega Alpha President

TRAINING
Resident in Pathology, Stanford University Hospital 1974-1976
includes six months Neuropathology with
L.J. Rubenstein and H. Urich
Fellow in Surgical Pathology, Stanford University Hospital 1976-1977
includes three months Hematopathology with
R.F. Dorfman
Postdoctoral Scholar (Clinical Cancer Grant), Stanford University Hospital 1977-1978
Training under Peter J. Scheuer, M.D., in Liver Pathology at Royal Free Hospital in London 8/77-9/77
Four weeks at AFIP with Kamal Ishak: Liver Pathology 9/79
Participation with Charles Carrington and Andrew Churg in evaluating pulmonary consultation material Endomyocardial biopsy review (primarily cardiac transplants) with back-up for Margaret Billingham, M.D. 1979-1983

LICENSURE AND CERTIFICATION
California: G30325 (Acquired 8/75) status-inactive (due to cost)
Utah: #7561 (Acquired 7/83) status-inactive (due to cost)
Minnesota: #0306717 (Acquired 1/87) status-active
Arizona: #D080 (Acquired 7/87) status-active
Florida: ME#0065410 (Acquired 12/93) status-inactive (due to cost)
American Board of Pathology Certification in Anatomic Pathology (5/27/78)

EMPLOYMENT, ACADEMIC APPOINTMENTS, AWARDS
Acting Instructor in Pathology Stanford University Medical Center 1978-1979
Acting Assistant Professor of Pathology Stanford University Medical Center 1979-1980
Assistant Professor of Pathology Stanford University Medical Center 1980-1983
Associate Professor of Pathology and Director of Surgical Pathology University of Utah College of Medicine 1983-10/86
Outstanding Teaching Award University of Utah Department of Pathology 1986
Camp Physician, Main Teen Camp, Kezar Falls, Maine 1 July 1985, 1986
Senior Associate Consultant in Surgical Pathology Mayo Clinic, Rochester, Minnesota 11/86-11/89
Associate Professor of Pathology Mayo Medical School, Mayo Medical Foundation 4/87-7/88
Dr. Abdul Rahman Jazieh is the Chairman, Department of Oncology, King Abdulaziz Medical City and a Professor at King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

He obtained his MD Degree from Damascus University, Syria and his Masters in Public Health from Tulane University, New Orleans. He completed his Fellowship in Hematology and Medical Oncology from University of Arkansas for Medical Sciences, Arkansas. He has American Boards of Internal Medicine, Hematology and Medical Oncology.

He was a Professor of Medicine and Director of Hematology Oncology Division at University of Cincinnati. Dr. Jazieh is a member of multiple US Professional society. He is a member of the International Affair Committee of ASCO.

Dr. Jazieh won multiple honors and awards including proclamation to the City of Cincinnati naming the day of January 5, 2006 as Dr. Abdul Rahman Jazieh Day.

He has numerous publications and many presentations in various meetings.

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Prof. Fouad Al Dayel, MD, FRCPA, FRCPath
Chairman, Department of Pathology and Laboratory Medicine
King Faisal Specialist Hospital & Research Centre
Riyadh, Saudi Arabia

CURRENT POSITIONS

Chairman
Department of Pathology and Laboratory Medicine
King Faisal Specialist Hospital and Research Centre
Riyadh, Saudi Arabia

Professor of Pathology
College of Medicine, Al Faisal University
Riyadh, Saudi Arabia

President
International Academy of Pathology (IAP) – Arab Division
(2010 – 2012)

OTHER TITLES:
Consultant Anatomic Pathologist (1995 to present)
Department of Pathology and Laboratory Medicine
King Faisal Specialist Hospital and Research Centre

Section Head, Molecular Genetics (2007 – 2011)
Department of Pathology and Laboratory Medicine
King Faisal Specialist Hospital and Research Centre

Corresponding Fellow for Saudi Arabia
Royal College of Pathologists of Australasia
(2004 – present)

Corresponding Member of the Board of Censors
Royal College of Pathologists of Australasia
(2005 – present)

Ex-Chairman, Arab School of Pathology
International Academy of Pathology (IAP) – Arab Division
(2003 – 2008)

SUBSPECIALTY INTERESTS:
Lung Pathology
Bone Pathology
Molecular Pathology
Stem Cell Therapy
Laboratory Quality Management and Accreditation

NO. OF PUBLICATIONS: 107
NO. OF ABSTRACTS: 141
Hanaa S. Bamefleh, MBchB, FRCPC, MME, FIAC, CPHHA
Deputy Chairman, Lab Education
Department of Pathology and Laboratory Medicine
King Abdulaziz Medical City
Riyadh, Saudi Arabia

Education:
Graduate with MBchB from King Abdul-Aziz University, Jeddah, Saudi Arabia.
Graduate from McGill University, Montreal Quebec, Canada with Canadian Board of Anatomic Pathology and fellowship in Pulmonary Pathology and Cytopathology.
Master of Medical Education, King Saud Bin Abdul-Aziz University for Health Sciences (KSAU-HS)

Current Positions:
Consultant of Anatomic Pathology and Pulmonary Pathology, Deputy Chairman, Department of Pathology and Laboratory Medicine (DPLM), King Abdul-Aziz Medical City (KAMC) Riyadh, Saudi Arabia.
Assistant Professor (KSAU-HS), Program Director, Clinical laboratory Science Program, KSAU-HS.
Chairperson Saudi Board of Anatomic Pathology, Saudi Commission for health Sciences (SCFHS)

Membership:
Fellow of the international Academy of cytology
Member Arab division of the International Academy of Pathology IAP
International Fellow, US-CAP
Member of Scientific committee of Saudi Society of Cytopathology
Member Saudi Lung Cancer Group
Member of Board of Registry for ASCP since 19 November 2008.
Member European Society of Pathology

Publication:
15 publications
7 abstract presentations
1. Adenocarcinoma in situ is recognized. Formerly many cases of were called bronchioloalveolar carcinoma (BAC).

2. Minimally invasive adenocarcinoma is recognized (less than 3.0 cm in diameter, lepidic predominant, 5 mm or less of invasion/central scar).

3. The term bronchioloalveolar carcinoma (BAC) is no longer used.

4. The new classification allows grouping stage 1 lung adenocarcinoma into three prognostic groups: one with a nearly 100% survival, one with approximately 60% 5-year survival, and an intermediate group with approximately 80-90% 5-year survival.

5. The micropapillary pattern is recognized as an unfavorable prognostic pattern.

6. The tumor formerly known as mucinous BAC is now recognized as a completely separate entity than non-mucinous BAC. Most tumors formerly called mucinous BAC are now called invasive mucinous adenocarcinoma.

7. The new classification has an emphasis on including in the pathology report all of the various patterns identified and their approximate proportions.

8. The importance of molecular testing in adenocarcinoma is emphasized, especially in advanced stage disease. Tests for EGFR and EML4-ALK are specifically mentioned.

9. In some cases histology may predict a molecular subtype. Signet ring cell change appears to be more frequent in ALK mutated tumors.

10. Given that there are definable subgroups of stage 1 adenocarcinoma with a very favorable prognosis, surgeons are now considering the possibility of sublobar resections in some cases.

11. The new adenocarcinoma classification includes recommendations for terminology in small biopsy specimens as well as resection specimens.

12. The term “non small cell carcinoma, not otherwise specified” is to be used as little as possible. If squamous or glandular features are not seen on H & E slides then immunostains looking for immunologic features favoring one or the other are recommended; e.g. CK 5/6, p63, TTF-1.
these cases, the tissue should be sent to molecular diagnostic studies. Those tumors that are positive for genetic abnormalities (positive for predictive biomarkers) will respond much better to targeted therapy.

Once the pathologists review the histology slides and diagnosis of NSCLC is confirmed, the distinction between squamous cell carcinoma from adenocarcinoma should be made. If this is not possible because the tumor is poorly differentiated, a limited panel of immunohistochemical (IHC) stains (e.g. TTF1, p63, p40) can be performed. It is important not to waste the tissue using large panel of IHC stains. The material should be saved for molecular testing especially for EGFR mutations and Alk gene rearrangement testing. If diagnosis is pure small cell carcinoma, pure squamous cell carcinoma or pure neuroendocrine carcinoma, then molecular testing is not recommended. However, for poorly differentiated carcinoma that cannot be classified or mixed tumors, tissue may be submitted for molecular studies also.

Testing for EGFR mutation and Alk rearrangement should be performed within two weeks of histological diagnosis. Targeted therapy can be used as first line therapy for Stage III or Stage IV disease. For Stage I and Stage II lung carcinoma, adequate tissue should be kept for possible molecular testing. Other option, molecular testing can be performed at time of diagnosis if cost is not a major issue.

**Tissue Management for Lung Adenocarcinoma**

Hanaa S. Bamefleh, MBchB, FRCPC, MME, FIAC, CPHHA - Riyadh,

Malignant lung specimens need to be handled by a competent pathologist with experience in pulmonary pathology. This early curtail initial step will ensure generation of state of the art slides and an accurate, comprehensive surgical pathology report that will characterize patient management and prognosis.

To ensure that a pathologist plays this role effectively and efficiently to generate accurate specific diagnostic reports, he/she has to be updated with all recent technology relevant to tissue handling, evaluation and interpretation.

Guidelines for handling lung malignancies are under continuous review and update by many study groups and centers to match the new molecular discoveries.

It is important for every anatomic pathology department to establish a definite protocol for each organ, and to come to an agreement with a multidisciplinary team, composed of a surgeon, a radiologist, a medical oncologist and a radiation oncologist before applying these guidelines to their oncology specimens. Regular updating of these guidelines with the most recent staging system and molecular markers that is useful for targeted therapy is crucial for up-to-date patient care and management.
Most problems will fall into the categories of colon:
Underdiagnosis – missing the carcinoma, calling it something less/benign.
Overdiagnosis – calling a metaplastic or reactive process carcinoma; overdiagnosis of indolent cancers.
Misdiagnosis – calling lung carcinoma some other tumor or incorrectly classifying lung carcinoma.

Underdiagnosis is complicated by small biopsy specimens and bland cytology, especially with mucinous tumors. Underdiagnosis may also be affected by obscuring inflammatory changes, necrosis, or fibrosis.

The key feature in identifying carcinomas with bland epithelium is monotony of cell type and finding an internal control of definite bronchiolar-type epithelium.
Overdiagnosis has included problems cytologically (squamous metaplasia, reactive type 2 cells), and histologically (frozen sections, type 2 cell hyperplasias, metaplasias) as well as benign tumors interpreted as carcinoma and carcinoid tumors overinterpreted as small cell carcinoma.

Metaplastic change is an important pitfall, both histologically and cytologically, and in the setting of an inflammatory process/pneumonia one should be very careful in making the diagnosis of carcinoma.

Trapped type 2 cells in a transbronchial biopsy may simulate lymphangitic growth.

Misdiagnosis of lung cancer can be misclassification of lung cancer or some other tumor as lung carcinoma (or vice versa). The first issue is small cell versus non small cell. The next issue is subclassification of nonsmall cell ca into squamous or adeno with either routine histology or immunohistochemical support.

The immunostains aren’t perfect and there are rare squamous carcinomas that are positive for TTF-1 and rare adenocarcinomas that are positive for CK 5/6.

TTF-1 may be positive in a number of non-lung and non-thyroid tumors, notably small cell carcinomas at a variety of sites.

**2012 Saudi Lung Cancer Management Guidelines**

**Abdul Rahman Jazieh, MD, MPH** - Riyadh, Saudi Arabia

Developing regional guidelines is important to incorporate pertinent local experience into the management recommendations, to ensure that every patient have the best management that can be offered according to available resources, to standardize cancer patient management, to improve available services for cancer care, to streamline cancer care funding and coverage, to reinforce multidisciplinary team work, to develop expertise in guidelines development/evidence based medicine and to encourage development of research projects.

Saudi Lung Cancer Guideline Committee is a multidisciplinary Committee composed of thoracic oncology experts from different institutions in the Kingdom that worked on developing and disseminating Lung cancer Management Guidelines since 2008. Saudi Lung Cancer Guidelines were published in the Journal of Infection and

The group members review the available guidelines, available evidence and regional experience then formulate recommendations with supporting manuscripts.

The guidelines are presented in a bullet format flow, addressing each stage separately, covering common scenarios and frequently encountered clinical situations.

The recommendations are based on the definitive tissue diagnosis, proper staging and patient evaluation. The goal is to offer the patient curative treatment whenever possible and if cure is not attainable then to help prolong survival or relieve symptoms and alleviate sufferings. The personalized therapy is emphasized strongly in these guidelines and this starts from the proper initial workup of the patients. Obtaining proper biopsy with adequate specimen is critical to determine subtype of lung cancer through IHC markers such as TTF1 CK 7, P63 then performing EGFR testing and ALK fusion tests. This highlights the importance of having proper tissue management plans. Taking into account tumor features, stage and patient’s performance status and condition, a selection of treatment can be made to provide personalized therapy.

In conclusion: the process of making guidelines highlights the value of interdisciplinary team work. The future challenge is how to assure implementation and monitoring of these guidelines.

**Differential Diagnosis of Mesothelioma**

Prof. Thomas V. Colby, MD, PhD - Arizona, USA

Mesothelioma is a histologic diagnosis. Radiologic and gross findings may be suspicious but the diagnosis is microscopic. Most cases of mesothelioma are associated with asbestos exposure or some other similar fiber, such as erionite.

Mesotheliomas have three basic patterns: epithelioid, sarcomatoid, and biphasic. Desmoplastic is a distinctive subtype that mimics scar tissue. A number of other unusual histologic patterns are recognized that pathologists should be familiar with (deciduoid, small cell, etc.).

A key feature in the histologic diagnosis of mesothelioma is whether one is dealing with an epithelioid proliferation or sarcomatoid proliferation.

For an epithelioid proliferation the major issues are benign versus malignant mesothelial cells; if cells are malignant then mesothelioma versus carcinoma (or other epithelioid tumor) becomes the issue.

Similarly, for spindle cell proliferations, the major distinction is between fibrous pleuritis and a neoplastic process. If it is neoplastic then it could represent sarcomatoid/desmoplastic mesothelioma or some other spindle cell malignancy involving the pleura.

A key feature in the diagnosis of most mesotheliomas is invasion of tissue: fat, skeletal muscle, lung. In the presence of a bulky mass lesion that is obviously a neoplasm, invasion becomes less important.

The most common problem is metastatic carcinoma versus mesothelioma; useful immunostains include the mesothelial markers Calretinin, WT-1, CK 5/6, D2-40, and carcinoma markers CEA, BerEp4, B72.3, MOC 31, TTF-1 and in specific situations, ER/PR, CDX-2, PSA.
Lymphoid tissue in the lung may be reactive or neoplastic. In some situations, particularly patients with Sjogren’s syndrome, indeterminate cases represent a real problem.

Lymphoid tissue in the lung, be it neoplastic or reactive, typically follows lymphatic routes which are regions where lymphatics are found: pleura, interlobular septa, along larger bronchovascular bundles.

Most of the original cases of lymphoid interstitial pneumonia (LIP) were probably diffuse lymphomas of the lung. Nevertheless, LIP is still reserved for cases that show dense (polytypic) lymphoid infiltrates and/or diffuse lymphoid hyperplasia (DLH).

The most common lymphoma in the lung is extranodal marginal zone B-cell lymphoma. These tumors may include a number of “benign” features including germinal centers, mixed infiltrates, granulomas, sclerosis.

Lymphomatoid granulomatosis is a distinctive form of lymphoma that includes prominent background T cells and a population of transformed B cells which represent the neoplastic cells and which can occasionally be shown to be monoclonal and which, by definition, show infection by EBV.

The morphology of LYG may be simulated in some post-transplant lymphoproliferative disorders and some iatrogenic lymphoproliferations (such as methotrexate-associated lymphoproliferation).

Common variable immunodeficiency (CVID) is recently recognized as involving the lung, typically as nodular infiltrates of lymphoid tissue that appears hyperplastic but is atypical for a lymph node. These patients typically have associated lymphadenopathy and splenomegaly. Granulomas may be associated with the infiltrates. The term “granulomatous lymphocytic lung disease (GLILD)” has been used. Patients who have CVID and GLILD have a worse prognosis than those who lack this form of lung disease.

IgG4-related disease is increasingly recognized in a number of sites including the lung. Pulmonary involvement in IgG4-related disease typically is seen as a mass lesion (resembling inflammatory myofibroblastic tumor) or as a patchy consolidative or more diffuse process that tends to show involvement of lymphatic routes by mixed infiltrates of inflammatory-appearing tissue rich in plasma cells. There is variable sclerosis. Infiltration of arteries, veins, and bronchioles is seen.
Case 1. Metastatic angiosarcoma.

The key features are nodular hemorrhagic regions with atypical cells that may or may not be intravascular. CD31 is the best stain to identify these cells. Some cytokeratin positivity may be present. Some sarcomatoid carcinomas may mimic angiosarcomas, notably pseudo angiomatous sarcomatoid carcinoma.

Case 2. Intravascular lymphomatosis.

The key features in this case are the very subtle infiltrates that need to be studied at high power in order to identify the atypical intravascular cells. CD20 is strongly positive and confirms the diagnosis. These patients typically present with skin or CNS disease but some present primarily with lung disease simulating interstitial lung disease.

Case 3. Ehler’s-Danlos syndrome.

The key feature in this case is the episodic history that includes hemoptysis and pneumothorax and focal lesions, including cystic change radiologically. The key histologic feature is the very distinctive tendon-like collagen that undergoes osseous metaplasia.

Case 4. Metastatic meningioma.

Metastases from “benign” tumors are recognized and have been seen with uterine leiomyomas, thymoma, mixed tumor of salivary gland, chondroblastoma, giant cell tumor of bone, meningioma, dermatofibroma, dermatofibrosarcoma protuberans and others.

Case 5. Synovial sarcoma.

The key point is that synovial sarcoma probably now represents the most common primary sarcoma of lung. The appearances are similar to soft tissue synovial sarcoma; most are monophasic. Most “sarcomas” of the lung in the past would probably be recognized as sarcomatoid carcinomas nowadays.

Case 6. IgG4-related disease.

Key features in this case are multi-site involvement (orbit and lung) and distinctly “inflammatory” appearance of the infiltrates although they show a distinct lymphangitic predilection, are very dense, and show prominent infiltration of arteries, veins, and airways.
Mission

To collaborate and lead national and international initiatives in lung cancer control including prevention, education, research and promotion of evidence-based practice.

Vision

Become a regional leader and global participant in the fight against lung cancer and contributor to the advancement of knowledge in the field.

Objectives

- Facilitate collaboration among health care professionals and organizations with interest in lung cancer
- Enhance evidence-based practice by the development, dissemination and implementation of guidelines relevant to the region
- Conduct research projects to help better understand and manage lung cancer in the region
- Participate in lung cancer control initiatives
- Conduct educational activities for health care professionals and the public
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