Spectrum of Benign Respiratory Cytology from Exfoliative to FNAs, Core needle Biopsies and EBUS

Dina R Mody, MD
Director of Cytology laboratories and Fellowship Program
Houston's Methodist Hospital and Bioreference Laboratory
The Ibrahim Ramzy Chair in Pathology
Department of Pathology and Genomic Medicine
Houston Methodist Hospital
Professor of Pathology and Lab medicine
Weill Cornell Medicine

For This session…….

- Types of Respiratory Specimens
- Types of Preparations
- Adequacy issues
- Infections
- Non neoplastic infiltrates
- Pitfalls…causes of false+ and false negatives
- Benign Neoplasms and non neoplastic masses
- Benchmarking/Interlaboratory comparison

Respiratory Cytology Indications

- To diagnose Infections (Fungal, Viral, others)
- Protocol BALs (s/p transplantation)
- Other non neoplastic, non infectious conditions
- Diagnosis of Cancer
- Staging of Lung cancer
- In inoperable cases or recurrence for diagnosis and molecular testing

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Types of Pulmonary Cytopathology

- Sputum
- Bronchial/Tracheal Brushings
- Bronchial Washings
- Bronchioloalveolar Lavage
- Fine Needle Aspiration Biopsy (Trans thoracic CT or US guided, TBNA, EBUS, Superdimensional Lung FNA
- Biopsies with Touch Preps for adequacy evaluation

Type of Specimen depends upon….

- Patient's clinical differential diagnosis (infection Vs tumor)
- Location of the lesion…….central vs peripheral
- Enlarged lymph nodes
- Diagnosis vs Staging vs additional testing
- Method of Procurement and who does the procedure (Pulmonologist vs Radiologist vs Surgeon)

Utilization Review and Reimbursement of Cytology Services In Endobronchial Ultrasound-Guided Procedures: Challenge and Opportunity

Ross A Miller MD, Angela M Wright MD, Laura S Satrum CT, Dina R Mody MD, Mary R Schwartz MD, Michael J Thrall MD

Houston Methodist Hospital, Houston Texas

ABSTRACT

A representative number of rapid on-site evaluations (ROSE) were documented for a three month time period at our institution (a quaternary care, 975 bed hospital). The case type and procedure along with time spent for travel, adequacy assessment, processing, screening, and sign out were recorded in order to assess time demands placed on staff by different procedures (Endobronchial ultrasound guided (EBUS), Computed Tomography-guided (CT), Ultrasound-guided (US), and Fluoroscopy guided). EBUS posed the greatest time challenges having the longest travel and processing times by cytotechnologists and longest adequacy assessment times by pathologists. Utilizing telecytology reduced the average time needed for adequacy assessment from 44.8 minutes to 24.6 minutes for EBUS procedures; advocating that telecytology can save time for the pathologist and make the service more cost-effective if the number of procedures is sufficient to justify investment in the technology.

INTRODUCTION

The roles of pathologist and cytotechnologists continue to evolve to optimize patient care, particularly with regard to ROSE. Having ROSE performed helps ensures sufficient material is obtained for diagnosis[1-7] and permits specimen triage for ancillary studies. At our institution, both on site and telecytology evaluations are increasingly utilized, particularly in EBUS. Consequently, time demands placed on the pathology and cytotechnology staff have exponentially increased creating workload management challenges.

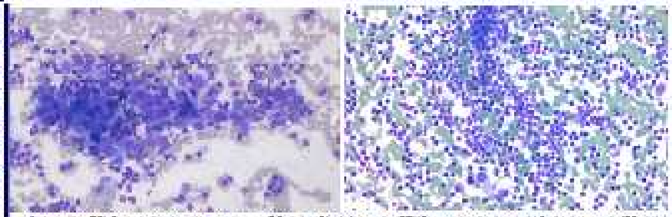
MATERIALS & METHODS

We representatively documented a number of ROSE for a three month period. Case type and procedure along with time spent for travel, adequacy assessment, processing, screening, and sign out were recorded in order to assess time demands placed on staff by different procedures (including EBUS, CT guided, US guided, fluoroscopy guided, and ocular). Because EBUS posed the greatest time challenges, cost and reimbursement differences were compared when telecytology was used and not used during EBUS adequacy assessment.

RESULTS

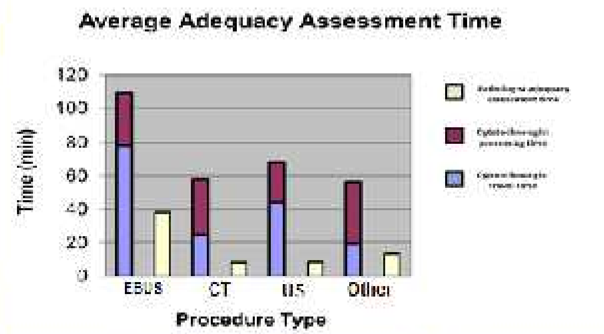
Average travel and processing time by cytotechnologists was variable among procedures (average 72.9 minutes) as was the adequacy assessment time by pathologists (average 16.9 minutes). EBUS posed the greatest time challenges with the longest travel and processing times (average 109 minutes) and longest adequacy assessment time (average 37.8 minutes). Using telecytology for EBUS procedures resulted in decreased adequacy assessment time (44.8 to 24.6 minutes on average) and a decreased net loss for the laboratory.

EBUS CASE EXAMPLES



Left: A positive EBUS case showing adenocarcinoma (DQstain). Right: A negative EBUS case showing lymphoid & blood elements (DQstain)

Average Adequacy Assessment Time



EBUS Procedure Cost and Reimbursement

	Technical Component	Professional Component	Global Component	Net Gain/Loss (range)
Reimbursement	**$46.73**	**$113.97**	**$160.70**	
Cost (using telecytology)	$109.00	$55.71 to $89.13	$164.71 to $198.13	**$-4.01 to $-37.43**
Cost (non-telecytology)	$109.00	$101.45 to $162.31	$210.45 to $271.31	**$-49.75 to $-110.61**
Cost (overall average)	$109.00	$85.00 to $136.95	$194.00 to $245.95	**$-33.01 to $-85.25**

DISCUSSION

From a work-management perspective, the provision of ROSE is challenging as reimbursement is low and time commitments are high. EBUS, compared to other procedures utilizing ROSE, is the most challenging as cytotechnologist travel and processing times take almost 40% longer and pathologist adequacy assessment time takes 3-4x longer. These increased time demands for EBUS are due to the targeting of multiple sites with associated procedural delays. Despite these workload management issues, ROSE is important for optimizing patient care as it helps ensure sufficient material is obtained for diagnosis[1-7] and permits specimen triage for ancillary studies. Telecytology has been shown to be a cost-effective alternative when distance and time-constraints are placed on the pathologist in certain settings[8,9]. Our data show that telecytology can make ROSE more cost effective in a large hospital setting when implemented in daily practice.

CONCLUSIONS

- Cytotechnologist travel and processing time for EBUS took almost 40% longer compared to other procedures.
- Pathologist adequacy assessment time for EBUS took 3-4x longer when compared to other procedures.
- ROSE reimbursement is low, and no greater for EBUS than other procedures. Use of telecytology can save time for pathologist and make the service more cost-effective if the number of procedures is sufficient to justify investment in the technology.

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ORIGINAL ARTICLE

Utilization review and reimbursement of cytology services in endobronchial ultrasound-guided procedures: challenge and opportunity

Ross A. Miller, MD[a,*], Angela M. Wright, MD[a], Laura S. Satrum, CT[b], Dina R. Mody, MD[c,d,e], Mary R. Schwartz, MD[d,f,g], Michael J. Thrall, MD[g,h,i]

[a] *Department of Pathology and Genomic Medicine, Houston Methodist Hospital, 6565 Fannin, M227, Houston, Texas*

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Specimen Preparations

- Smears
- Cytospins
- ThinPreps
- SurePath
- Cell blocks (various types)

Respiratory, Adequacy

- Adequate if it explains the clinical condition
- Sputum - Alveolar macrophages, no numerical cut point.
- Bronchial wash & brush - Cells or agents diagnostic of a pathologic process are present.
- Well preserved, optimally stained ciliated columnar cells, goblets and macrophages.
  - *Respiratory Specimen Guidelines. Modern Pathology. 1999: Vol 12;427*

Continued

- BAL -Adequate if demonstrates specific pathologic process
- Numerous alveolar macrophages(93+/-5%) and few lymphocytes(7+/-1%). Occasional neutrophils and rare ciliated or squamous cells

Respiratory Adequacy

continued

BAL(Chamberlain et al) Inadequate if:

- Paucity of alveolar macroph (<10/10hpf or <25/hpf with*
- *excess epithelial cells, degenerative changes or > # of macrophages
- *Mucopurulent exudate of PMNs
- RBCs, degn changes,artifacts

Acta Cytol 1987;31:599

Unsatisfactory BAL

- Paucity of alveolar macrophages(<10/hpf)
- Too many ciliated or squamous cells
- Mucopurulent exudate(polys)
- Degenerated cells and lab artifacts
- *By Chamberlain et al.Acta cytol 1987;31:599*

Respiratory FNAs (any type)

- Cells that explain the radiographic and clinical presentation
- Alveolar macrophages, mesothelial cells, resp epithelial cells…not enough
- Lymphocytes if EBUS of peribronchial lymph node
- Diagnostic tissue i.e carcinoma, granuloma
- Blood, low cellularity, tracheobronchial secretions air drying etc contribute to unsatisfactory

Sensitivity, Specificity, PPV, NPV of Different Specimen types (%) for Neoplasms

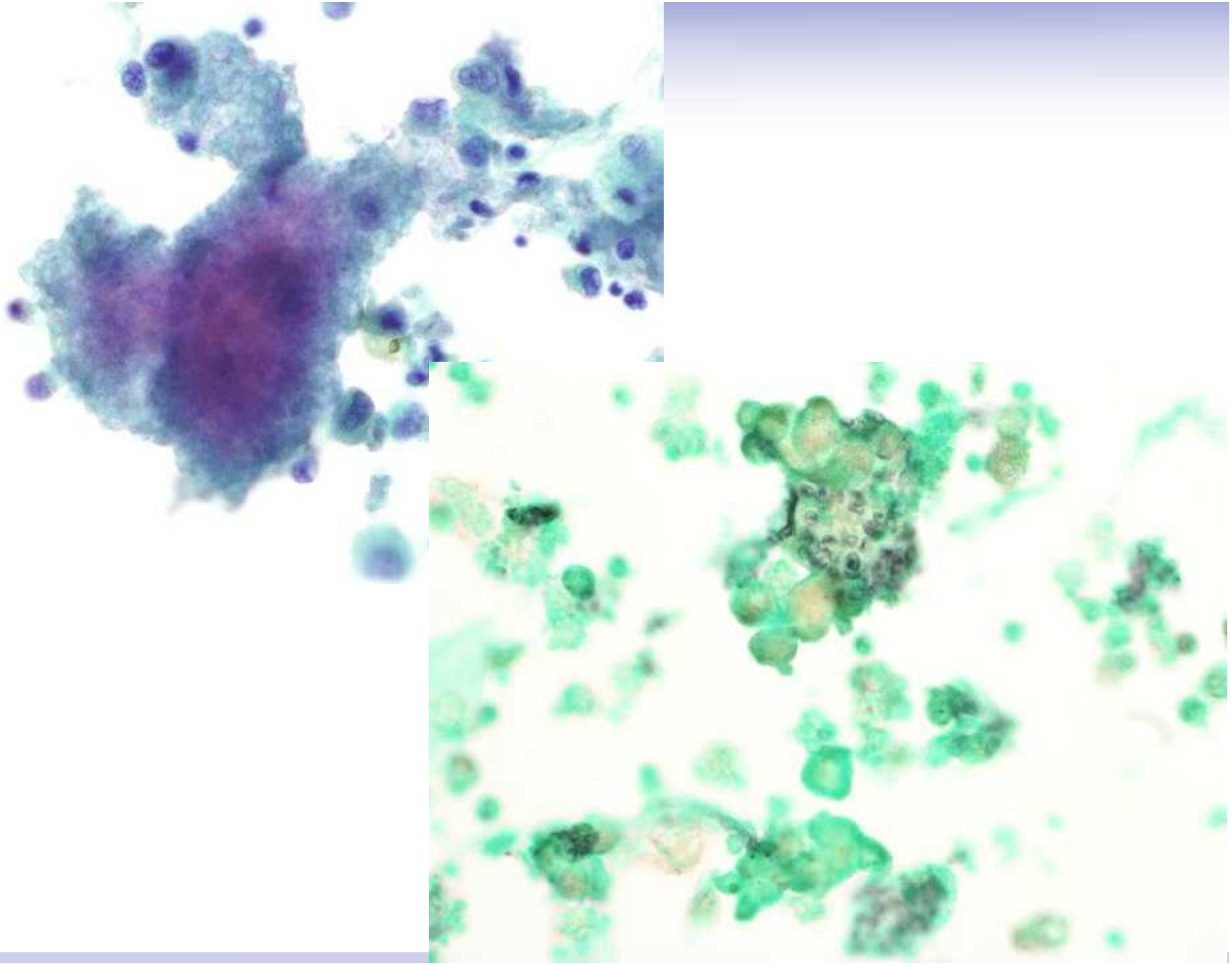
Specimen Type	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Sputum	42/91 (5 specs)	96-99+	100	15
Bronchial Brush	59 (C)/52 (P)	98+		
Bronchial Wash	48 (C)/33 (P)	99+		
BAL	40 (C)/37 (P)	99+		
Transthoracic FNA	82-89	96-100	98-100	70-77
Endobronchial FNA	56	74	100	53-70
EBUS W ROSE*	88	98	71	98
EBUS no ROSE*	80	97	76	98

PPV=Positive predictive value
NPV=Negative Predictive value
ROSE=Rapid on site evaluation

** Micames et al. Chest 131/2/2007 pgs 539-548*

Case 1

50 yr old male with h/o treatment for lymphoma and cough, weight loss and a radiographic infiltrate. Bronchoscopy with washings, BAL and brushings performed.



FUNGAL ORGANISMS IN RESPIRATORY CYTOLOGY

Key Facts

Cytopathology

- *Aspergillus*-like hyphal fungi have septate straight-edged hyphae (3-6 µm) with acute-angle branching
- *Zygomyces/Mucor* have ribbon-like wavy-edged non-septate hyphae (4-15 µm) with right-angle branching
- *Candida* species, usually contaminants in lung specimens, have yeast or pseudohyphal forms
- Major infectious yeasts include *Cryptococcus*, *Histoplasma*, and *Blastomyces*
  - These can be differentiated by size, shape, budding pattern, and encapsulation

Ancillary Tests

- Gomori methenamine silver improves sensitivity and morphologic characterization
- Mucicarmine highlights capsule of *Cryptococcus*

Comparative Features of Dimorphic Fungi

Fungus	Size	Reproduction	Distinctive Feature
Cryptococcus neoformans	Variable (3-20 µm)	Narrow-based budding	Mucicarmine-positive capsule
Histoplasma capsulatum	Small (3-5 µm)	Narrow-based budding	Always intracellular
Blastomyces dermatiditis	Large (10-25 µm)	Broad-based budding	Thick walls
Coccidioides immitus	Large spherules (10-60 µm)	Endospores within spherules	Empty ruptured spherules
Paracoccidioides brasiliensis	Large spherules (10-50 µm)	Peripheral buds on spherules	"Mariner's wheel" budding pattern
Penicillium marneffei	Small (2-6 µm)	Fission rather than budding	Central septation of yeasts
Sporothrix schenckii	Small (2-8 µm)	Round-to-oval buds	Elongated "cigar bodies"

Chapter by Thrall MJ in Diagnostic Pathology: Cytopathology Ed Mody, Amirsys 2014

Pulmonary Fungal Infections

Fungus	Morphology	Size(D)
Crypto	Yeast mucin,broad based buds	4-15micron
Aspergillus	septate hyphae 45 degree branching	5-10 mic
Phycomycosis (Mucor)	non septate hyphae 90 degree branching ribbon like	10-30 (Wide)
Candida	budding yeast pseudohyphae sausage like	2-10

Pulmonary Fungal Infections

Fungus	Morphology	Size(D)
Histo	Yeast small,budding,intracellular	1-5micron
Coccidiomycosis	spherules endospores	15-60 mic 1-2 micr
Blastomycosis	broad based budding yeast, thick cell wall	8-20 micr
Sporotrochosis	Intracellular ovoid yeast with slight halo	2-4micr

Aberrant Staining with Gomori's Methenamine Silver: Utility Beyond Fungal Organisms

Angela M. Wright, MD; Dina R. Mody, MD; Mary R. Schwartz, MD; Rose C. Anton, MD.
Department of Pathology & Genomic Medicine, The Methodist Hospital, Houston, TX.

ABSTRACT

BACKGROUND: Historically, Gomori's methenamine silver (GMS) stain has been used in cytopathology preparations to highlight *Pneumocystis jirovechi*, as well as other fungal organisms including *Cryptococcus*, *Candida*, *Histoplasma*, *Blastomycosis*, and *Aspergillus*. However, several non-fungal organisms can show distinct staining patterns with GMS that are important to recognize.

MATERIALS AND METHODS: We prospectively and retrospectively identified non-fungal pathogenic organisms on GMS-stained ThinPrep and cytospin preparations of recent bronchioloalveolar lavage and bronchial wash cytologic specimens. The organisms included parasitic worms, virus, acid-fast, partially acid-fast bacilli and nonacid-fast bacteria. Six cases were identified, including two cases of *Strongyloides stercoralis*, one case of Cytomegalovirus, one case of *Mycobacterium tuberculae*, one case of *Nocardia species*, and one case of anthrax – like *Bacillus cereus*. Staining patterns were recorded.

RESULTS: The non-fungal organisms in all six cases had silver deposition in varying locations with GMS stain. The GMS strongly stained the internal organs of *Strongyloides stercoralis* larvae and/or the cuticle. Intranuclear cytoplasmic inclusions of Cytomegalovirus-infected cells stained positively with the GMS stain. The surface of extracellular filamentous partially-acid fast *Nocardia species* and the small intracellular acid-fast *Mycobacterium tuberculae* were highlighted with GMS stain. The cell wall and the central endospores of *Bacillus cereus* were delineated by GMS and easily visualized by light microscopy. In three of the six cases, these organisms were not clinically suspected. However, it was the aberrant GMS staining that pointed to the diagnosis and resulted in the performance of the definitive stain or test/cultures.

CONCLUSION: GMS is a chromic acid, sodium bisulfate stain that is known to precipitate silver ions within fungal polysaccharide walls, producing the characteristic black stain seen by light microscopy. In addition to *Pneumocystis jirovechi* and other fungi, we have found that GMS also stains several additional human pathogens, including various acid-fast, partially acid-fast, and non-acid fast bacteria; parasitic organisms; and virally infected cells. It is imperative to recognize aberrant GMS staining in order to avoid misdiagnosis of fungal elements. By highlighting several pathogenic non-fungal organisms, this stain may be a particularly useful diagnostic aid when the infectious condition is not clinically suspected or the number of organisms present is sparse and otherwise difficult to visualize by routine staining methods such as the Pap stain.

INTRODUCTION

Fungal organisms including *Pneumocystis jirovechi*, *Cryptococcus*, *Candida*, *Histoplasma*, *Blastomycosis*, and *Aspergillus* can be detected in cytopathology preparations using Gomori's methenamine silver (GMS) stain. However, several non-fungal organisms can have distinct staining patterns with GMS which are important to recognize to avoid misdiagnosis as fungal elements.

MATERIALS & METHODS

Non-fungal pathogenic organisms which were highlighted on GMS-stained ThinPrep and cytospin preparations of bronchioloalveolar lavage and bronchial wash cytologic specimens from 2011 – 2012 were retrospectively and prospectively identified. The organisms included parasitic worms, virus, acid-fast, partially acid-fast bacilli and nonacid-fast bacteria.

Six (6) cases were identified:
- Two (2/6) *Strongyloides stercoralis*
- One (1/6) Cytomegalovirus
- One (1/6) *Mycobacterium tuberculae*
- One (1/6) *Nocardia species*
- One (1/6) anthrax – like *Bacillus cereus*[1].

Staining patterns were recorded.

RESULTS

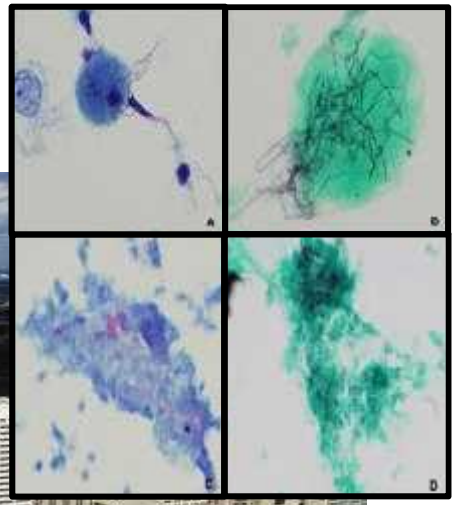
The organisms in all six cases (6/6) had silver deposition in varying locations within the cell (Table 1). The surface of extracellular filamentous partially-acid fast *Nocardia species* and the small intracellular acid-fast *Mycobacterium tuberculae* were highlighted with GMS stain (Figure 1). The GMS strongly stained the internal organs of *Strongyloides stercoralis* larvae and/or the cuticle (Figure 2). Intranuclear cytoplasmic inclusions of Cytomegalovirus-infected cells stained positively with the GMS stain (Figure 3). The cell wall and the central endospores of *Bacillus cereus* were delineated by GMS and easily visualized by light microscopy (Figure 4).

In three of the six cases (3/6), including *Nocardia*, *Strongyloides stercoralis,* and anthrax-like *Bacillus cereus,* organisms were not clinically suspected. However, it was the aberrant GMS staining that pointed to the diagnosis and resulted in the performance of the definitive stain or test/cultures.

TABLE 1

ORGANISM	GMS STAIN LOCALIZATION
Strongyloides stercoralis	**Internal organs and cuticle**
Cytomegalovirus	**Intranuclear inclusions**
***Nocardia* species**	**External surface**
Mycobacterium tuberculae	**External surface**
Bacillus cereus	**Cell wall and central endospores**

FIGURE 1

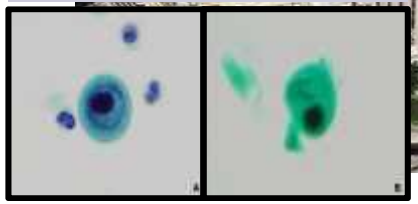


Nocardia species (40x: A. Fite modified acid-fast stain, B. GMS stain); *Mycobacterium tuberculae* (20x: C. Kinyoun acid-fast stain, D. GMS stain)

FIGURE 2

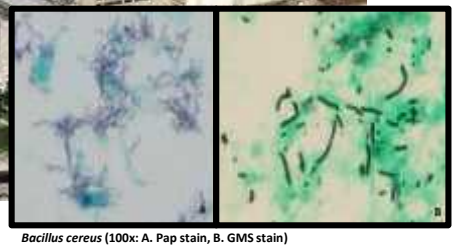
Strongyloides stercoralis (20x: A. Pap stain, B. GMS stain)

FIGURE 3



Cytomegalovirus (100x: A. Pap stain, B. GMS stain)

FIGURE 4



Bacillus cereus (100x: A. Pap stain, B. GMS stain)

DISCUSSION

GMS is a chromic acid, sodium bisulfate stain that is known to precipitate silver ions within fungal polysaccharide walls, producing the characteristic black stain seen by light microscopy.

In addition to *Pneumocystis jirovechi* and other fungi, we have found that GMS also stains several additional human pathogens including various acid-fast, partially acid-fast, and non-acid fast bacteria; parasitic organisms; and virally infected cells.

An extensive literature review of peer-reviewed journals and cytopathology textbooks shows only one article discussing GMS positive CMV inclusions[2]; there is otherwise a paucity of published information regarding aberrant GMS staining in non-fungal organisms.

CONCLUSION

The recognition of aberrant GMS staining is imperative in order to avoid misinterpretation of non-fungal organisms as fungal elements.

By highlighting several pathogenic non-fungal organisms, this stain may be a particularly useful diagnostic aid when the infectious condition is not clinically suspected or the number of organisms present is sparse and otherwise difficult to visualize by routine staining methods such as the Pap stain.

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No relationship exists that represents a possible conflict of interest with respect to the content of this presentation.

Bronchial Washings: General Dx: Neg. Reference DX: Fungal

General Diagnosis(Lab)

Pos	Neg/Bn	Susp/Pos	Usat
2.8%	94.4%	0%	2.8%
0.9	95.6	2.7	1.8

Ref Dx	Lab	PTH	CT
Fungal	69.4%	69%	78.6%
Fungal	74.3	83.1	83.2
PAP	8.3%	13.8%	5.4%

CAP Interlaboratory Comparison program in Non gyn cytology 2002 and 2010 data

BAL: General Dx: Neg. Reference DX: Fungal Infection

General Diagnosis(Lab)

Pos	Neg	Susp	Usat
0%	100%	0%	0%

Ref Dx	Lab	PTH	CT
Fungal	100%	88.9%	76.5%
Nl/Reactive	0%	3.7%	17.6%

BAL: General Dx: Neg. Reference DX: PCP

General Diagnosis(Lab)

Pos	Neg	Susp	Usat
0.7%	98.6%	0.2%	0.5%
Ref Dx	**Lab**	**PTH**	**CT**
Fungal	1.2%	2.8%	4.2%
Nl/Reactive	0.9%	0.9%	3.7%
PCP	91.2%	93%	88.1%

CAP Interlaboratory comparison Program in Non Gyn Cytology data for 2012

Case 2

37 yr old male, with shortness of breath and pulmonary infiltrates. Bronchoscopy with washings, brushings and BAL performed.

Differential of Amorphous Material in Respiratory Specimens

- Pneumocystis Jiroveci (PCP)
- Pulmonary Alveolar Proteinosis
- Microliths and Psammoma bodies
- Fibrin
- Hemorrhage
- Amyloid
- Aspirated material

Pulmonary Alveolar Proteinosis

- Seen in people exposed to fine dusts, altered immunity/immunosuppression, Rx for hematopoeitic malignancies
- More recently, post transplant drug Rx
- Alveoli filled with fine granular frothy material with darker globs of eosinophilic material and cholesterol clefts, macrophages
- PAS +, Diastase resistant
- Deactivated Surfactant (EM-lamellar myelin bodies)

Pulmonary Alveolar Proteinosis

- Impaired alveolar macrophage function caused by neutralizing anti-granulocyte macrophage colony stimulating autoantibodies(anti-GM-CSF)
- Dx and RX BAL
- Sub cutaneous GM-CSF x 12 WKS
- Repeat BAL

Pulmonary Alveolar Proteinosis

- Final common expression of abnormalities of pulmonary surfactant and pulmonary immune function
- Inherited or acquired mutations
- Deficiency of surfactant proteins
- Impaired function of granulocyte-macrophage colony-stimulating factor (GM-CSF)

Pulmonary Alveolar Proteinosis

- Three Subgroups
  - Idiopathic (acquired/adult-type): 90%
  - Secondary: 5%-10%
  - Pediatric: 2% Rare juvenile and familial cases, some may be same as chronic pneumonitis of infancy
  - ¾ of idiopathic and secondary PAP patients are tobacco smokers; male:female = 3:1

Idiopathic PAP

- 90% of cases
- Worldwide prevalence of 3.7 cases/million persons
- Autoantibodies against GM-CSF
  - Impair GM-CSF terminal differentiation of alveolar macrophages
  - Results in impaired clearance of surfactant from lung
  - Also impair antimicrobial activity of GM-CSF

Secondary PAP

- 5%-10% of cases
- Dust exposures: Silica, cement, aluminum, titanium dioxide, nitrogen dioxide, fiberglass
- Hematologic malignancies:Leukemia, Lymphoma
- Immunodeficiency: HIV, transplant patients, cytoxic and immunosuppressive therapy

PULMONARY ALVEOLAR PROTEINOSIS AND MIMICS

Key Facts

Clinical Issues
- Respiratory distress due to alveoli filled with proteinaceous material secondary to macrophage dysfunction or surfactant excess
- Usually autoimmune but also seen in association with immunosuppression, hematologic malignancies, inhalational exposures, congenital syndromes

Cytopathology
- Abundant proteinaceous material in the background
- Globular homogeneous structures
- Alveolar macrophages also contain proteinaceous debris in cytoplasmic vacuoles

Ancillary Tests
- Periodic acid-Schiff (PAS)

Top Differential Diagnoses
- *Pneumocystis* pneumonia
- Necrosis
- Corpora amylacea

Background
- Proteinaceous material
  - Globular homogeneous structures
    - Alcohol fixation enhances this appearance
  - Scattered granular debris

Cells
- Alveolar macrophages also contain proteinaceous debris in cytoplasmic vacuoles

MACROSCOPIC FEATURES

Corpora Amylacea
- Glycoprotein globules with faint concentric rings, positive for PAS
  - Usually few, weakly polarizable

Amyloid
- Rarely forms distinct globules
- Congo red birefringence

Amiodarone Toxicity
- Lamellated inclusions in macrophages;
- Lacks globules

Chapter by Thrall MJ in Diagnostic Pathology: Cytopathology Ed Mody, Amirsys 2014

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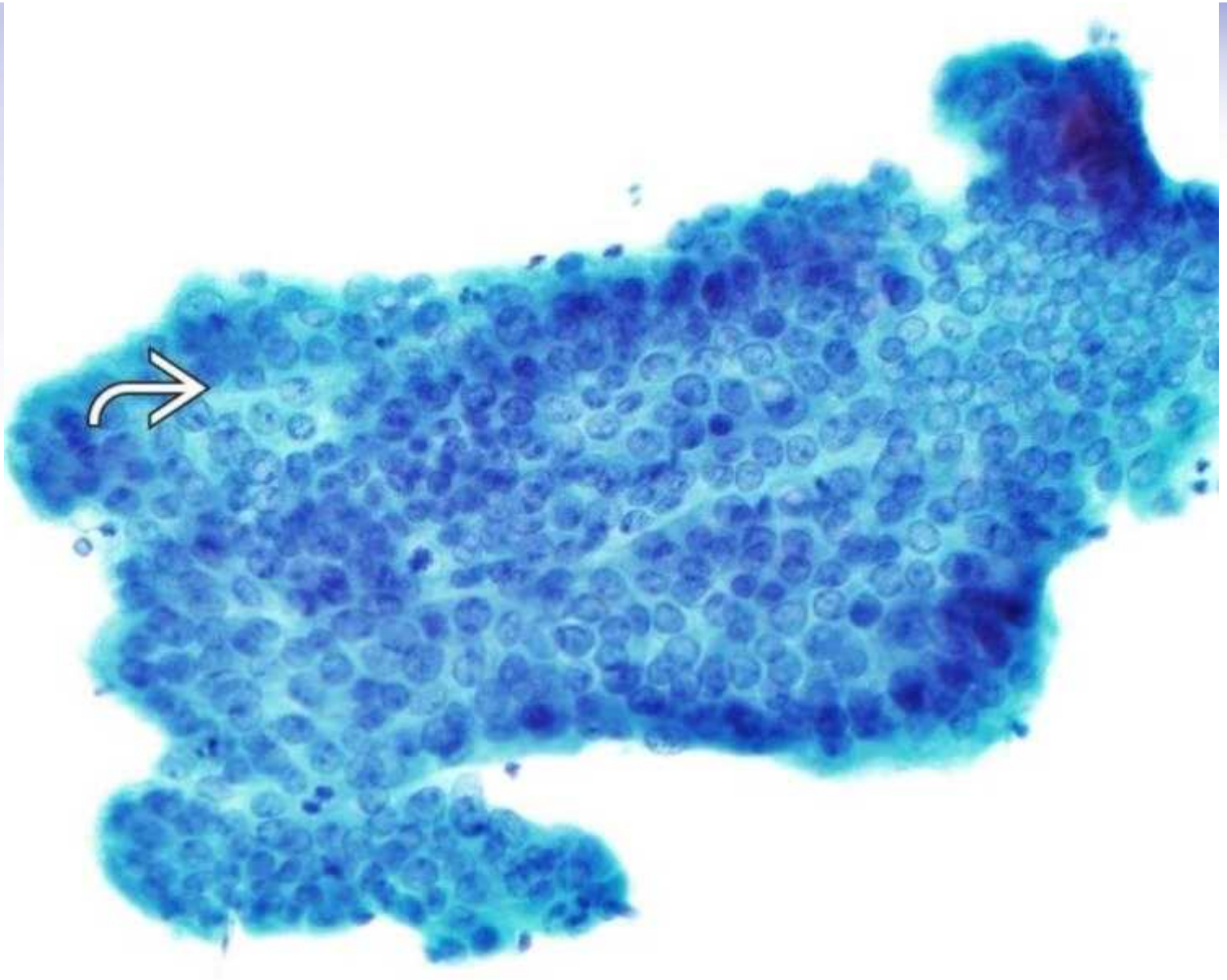

Well-differentiated adenocarcinoma shows minimal architectural disorder (white curved arrow) and nuclear changes, making separation from a reactive process difficult, even in well-visualized Pap-stained examples.

Cytology Picture from Chapter by Thrall MJ in Diagnostic Pathology: Cytopathology Eds Mody, Amirsys 2014

Mimicks of Pulmonary Carcinoma

- Repair/reactive
- Creola Bodies (bronchial hyperplasia)
- Squamous metaplasia with atypia (due to radiation or other treatment)
- Organizing Pneumonia and Pulmonary Infarcts….can be outright dangerous!
- Abscess cavity lining

Benign /Reactive Vs Malignant

Benign/Reactive/Mimicks	Adenocarcinoma or Squamous ca
Orderly groups	Disorderly groups
Some nuclear enlargement, Hypochromatic or euchromatic	Marked Nuclear enlargement, Hyperchromatic
N/C ratio maintained.	N/C ratio increased.
Smooth nuclear membranes	Irregular nuclear membranes
Regular micronucleoli	Irregular or macronucleoli
Terminal bars and cilia	None or very focal cell T bars and cilia
No Diathesis	Diathesis
Rare and normal mitosis	Frequent and abnormal mitosis

Partly Abbreviated from DeMay Art and science of cytopathology, 2nd edition

Causes of False Positive Diagnosis

- Reactive Type 2 Pneumocytes
- Reactive Bronchial epithelium
- Reserve cells
- Cavitary lesions
- Granulomas
- Mesothelial cells
- Contaminants
- Benign neoplasms

Atypical Cells in Bronchoalveolar Lavage Specimens From Bone Marrow Transplant Recipients

A Potential Pitfall

H. Evin Gulbahce, MD,[1] K. Scott Baker, MD,[2] Pragati Kumar, MD,[1] Klint Kjeldahl, CT(ASCP),[3] and Stefan E. Pambuccian, MD[1]

Key Words: Bronchoalveolar lavage; BAL; Bone marrow transplant; BMT; Atypical

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Abstract

Numerous nonneoplastic conditions of the lungs may result in atypical cells in bronchoalveolar lavage (BAL) specimens mimicking malignant neoplasms. Bone marrow transplant (BMT) recipients have many predisposing factors that would lead to atypical cells in BAL specimens, presenting diagnostic challenges. We

Bone marrow transplant (BM
therapy for patients with hematol
certain congenital disorders, ar
Pulmonary complications after B
up to 60% of the patients and incl
graft-vs-host disease (GVHD), ar
to conditioning therapy.[1-3] Bron

Gulbache E et al Am J Clin Pathol Vol 120(1) 101-6. 2003

NONGYNECOLOGIC CYTOPATHOLOGY

Cytologic Findings in Allogeneic and Autologous Bone Marrow Transplant Patients with Pulmonary Symptoms

A 9-Year Follow-up Study

Ognjen Kosarac, M.D., George Carrum, M.D., Dina Mody, M.D., and Hidehiro Takei, M.D.

Objective

To evaluate cytologic findings in patients who underwent bone marrow transplant (BMT) and correlate with the clinical, radiologic and histologic findings.

Study Design

Cytologic findings of the BMT patients with pulmonary symptoms from 1994 to 2007 were reviewed for the presence of malignancies, infectious organisms, inflammation and reactive changes, including treatment-related cellular atypia. Corresponding clinical

Reactive bronchial epithelial cells were found in 4 specimens and reactive squamous cells in 1 specimen. Four patients had markedly atypical cells in 4 specimens—atypical epithelial and mesothelial cells in 3 and 1 specimens, respectively. No malignancy was seen in any specimens examined. Acute inflammation was present in 6 specimens. Candida was the most common microorganism found (11 specimens). The cytologic findings were felt to correlate with clinical and radiologic findings and histologic follow-up.

It is important to be aware of the range of cellular atypia in various cytology specimens and their associated clinical conditions.

Kosarac O, Carrum G, Mody D & Takei H. Acta Cytol Vol 53(5) 565-70. 2009

How do you tell reactive type 2 Pneumocytes with Atypia?

- History: Patients ill with “pneumonia” or whited out lungs or have chronic disease which is worsening
- Few cell groups
- Hypocellular, few clusters
- Few single atypical cells
- Background inflammation or hemorrhage
- Smudged nuclei

How do you tell reactive type 2 Pneumocytes with Atypia?

- History: Pneumonia
- ARDS
- Chemotherapy/XRT
- Oxygen therapy
- AIDS
- Idiopathic pulmonary fibrosis
- No distinct mass…more pneumonia like

Causes of False Positive Diagnosis

- Reactive Type 2 Pneumocytes
- Reactive Bronchial epithelium
- Reserve cells
- Cavitary lesions
- Granulomas
- Mesothelial cells
- Contaminants
- Benign neoplasms

Causes of False Positive Diagnosis

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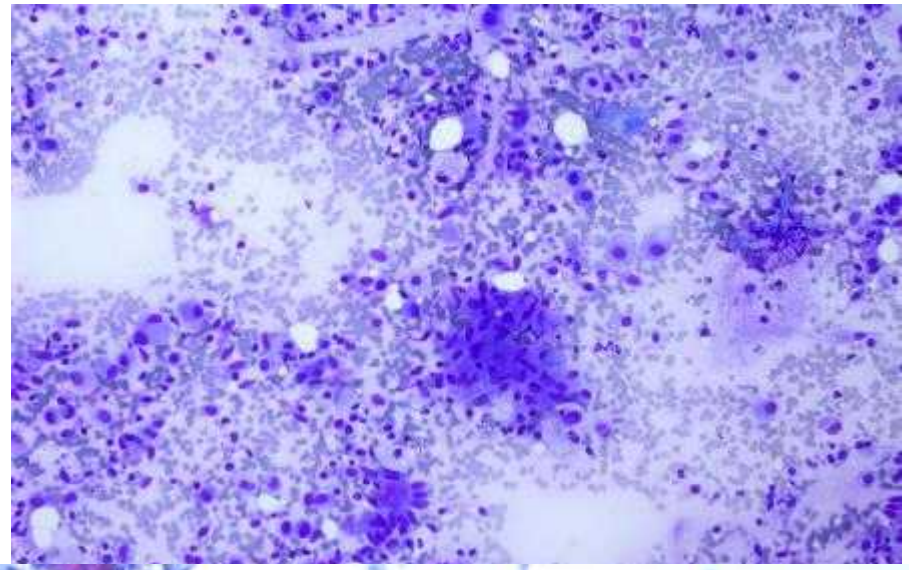
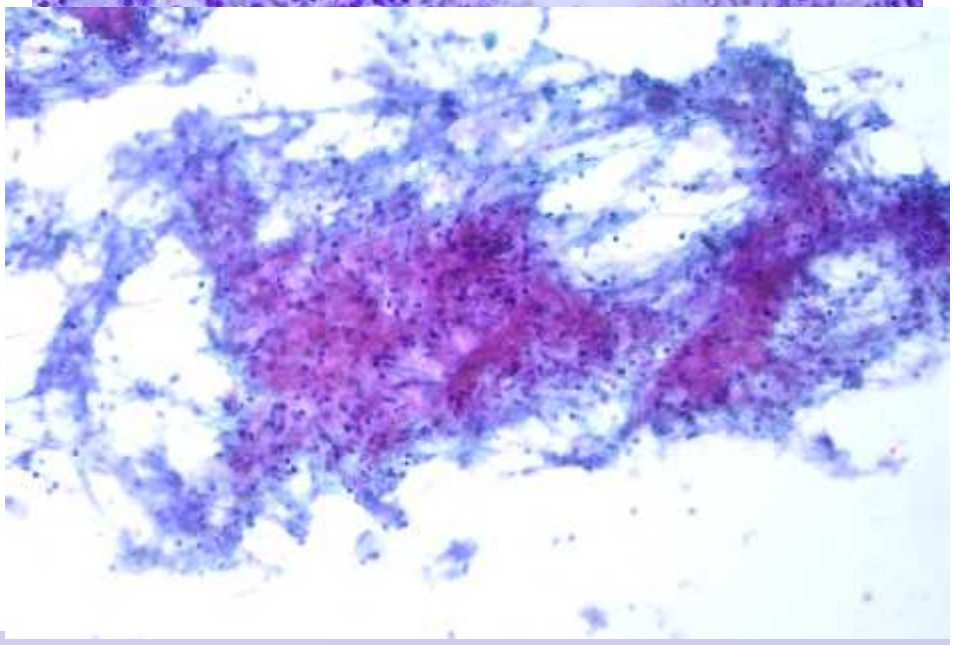
Cytologic Features of Granulomas

- Aggregates of Histiocytes
- Syncytial arrangement, no cell boundaries
- Vesicular and boomerang nuclei
- Vesicular and elongated nuclei
- Scattered lymphocytes
- Necrosis, organisms, +/-





Changes Associated With Radiotherapy

- Cytomegaly with bizzare shapes
- Nuclear and cytoplasmic enlargement
- Multinucleation
- Nuclear and cytoplasmic vacuolization
- Repair like changes

Greatest Potential for Mis diagnosis

- Granulomatous Inflammation
- Organizing Pneumonia
- Therapy effect(XRT/Chemotherapy)

RARE BENIGN AND LOW MALIGNANT POTENTIAL TUMORS

Key Facts

Clinical Issues

- Hamartoma results from overgrowth of mature mesenchymal elements
- Sclerosing hemangioma arises from pneumocytes though lesions resemble vascular tumors
- Solitary fibrous tumor usually arises from pleura but may arise elsewhere and is not always single
- Clear cell (sugar) tumor arises from perivascular epithelioid cells (PEComa)

Cytopathology

- Hamartoma consists of mixed benign stromal and glandular elements
- Sclerosing hemangioma neoplastic pneumocytes form loose clusters surrounding stromal cores
- Solitary fibrous tumor features bland spindle cells with collagen in background
- Clear cell (sugar) tumor consists of bland cells with abundant finely vacuolated glycogen-rich cytoplasm

Characteristics of Benign and Low Malignant Potential Tumors of Lung and Pleura

Tumor	Clinical/Radiologic Features	Cytologic Features	Helpful Stains
Hamartoma	Incidental "popcorn" lesion, lobulated but well demarcated	Mixed benign cartilaginous and glandular elements, fibrillary matrix	Romanowsky highlights cartilaginous matrix
Sclerosing hemangioma (pneumocytoma)	Incidental "coin" lesion, usually female	Loose clusters surrounding stromal cores, fine chromatin, nuclear pseudoinclusions	TTF-1 positive, negative for vascular markers
Solitary fibrous tumor	Pleural-based, well-circumscribed tumors	Uniform bland spindle cells, ropey collagen fragments	CD34 and Bcl-2 positive, S100 and cytokeratin negative
Clear cell (sugar) tumor	Incidental "coin" lesion; may be associated with tuberous sclerosis or other perivascular epithelioid cells	Bland cells with finely vacuolated cytoplasm, naked nuclei, transgressing vessels	PAS highlights cytoplasmic glycogen, HMB-45 positive
Granular cell tumor	Endobronchial, possibly with obstruction	Polygonal epithelioid cells with abundant granular cytoplasm and small bland nuclei	PAS highlights granules, S100 positive
Salivary gland analog tumors	Endobronchial, possibly with obstruction	Same as salivary gland counterparts	Diff-Quik highlights stroma of pleomorphic adenoma

Chapter by Thrall MJ in Diagnostic Pathology: Cytopathology Ed Mody, Amirsys 2014

Pulmonary Cartilaginous Hamartoma

- Most common Benign lung tumor, M>W
- Characteristic Radiographic appearance, 1-5cms, peripheral
- Mixture of cartilage, adipose tissue and respiratory epithelium, may calcify/ossify
- Distinctive clonal cytogenetic aberrations
- Resection is curative

Pulmonary Cartilaginous Hamartoma

- Aspirate similar to Pleomorphic Adenoma of salivary glands
- Chondrocytes, adipose tissue and varying amounts of respiratory epithelial elements are admixed
- Brilliant magenta staining of chondroid matrix on DQ stain.
- Chronic inflammation and smooth muscle also may be seen

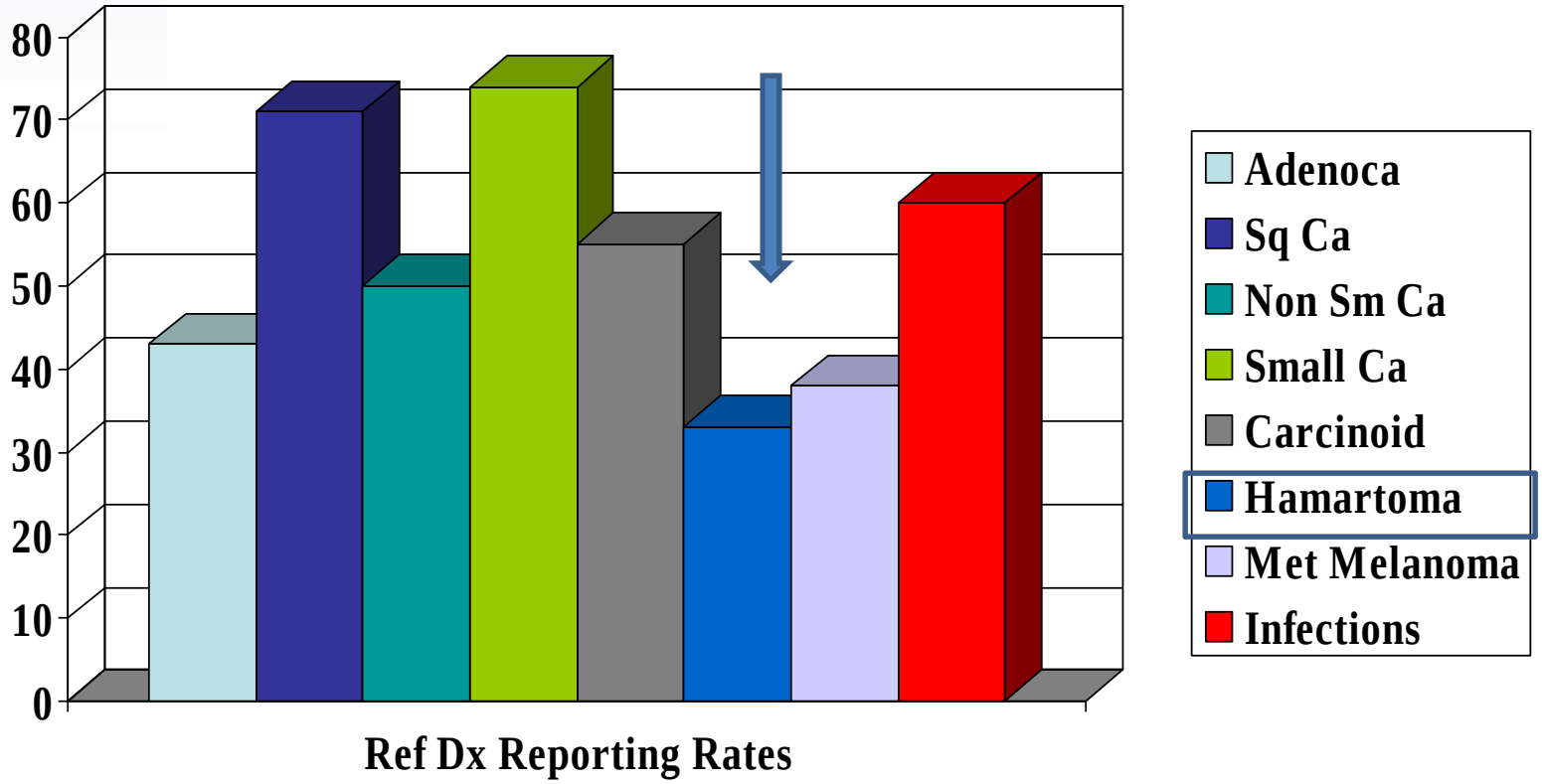
CAP Non Gyn program Lung FNA General Dx: Negative/Benign Reference DX: Hamartoma

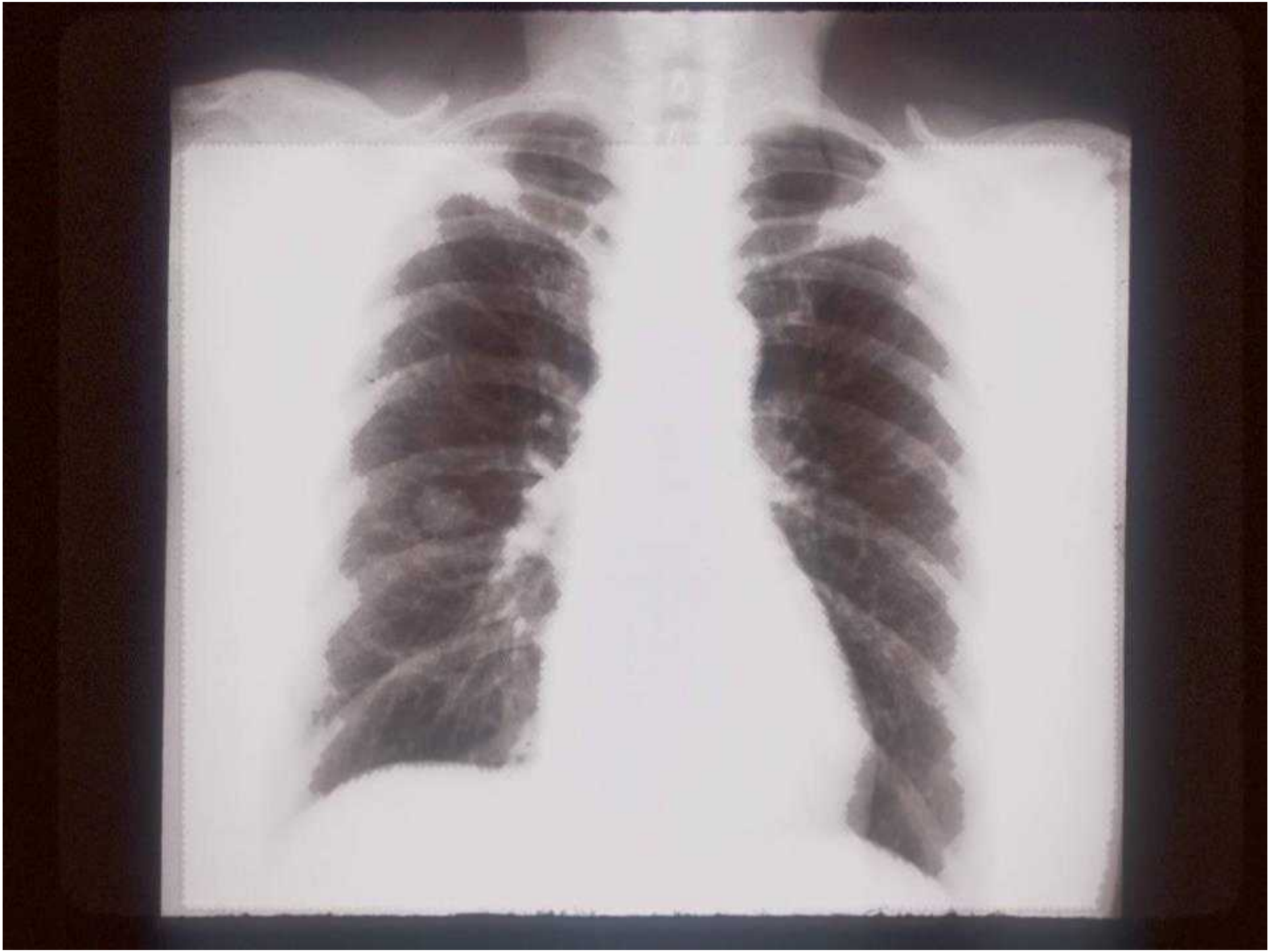
General Dx	Pos	Neg/Benign	Susp
(Lab)	13.6%	78%	5.1%

Ref Dx	Lab	PTH	CT
Hamartoma	42.4%	37.4%	22.5%
Bn Lesion	15.3%	18.7%	15.5%
Normal	13.6%	8.4%	31%

CAP Interlaboratory comparison program in Non Gyn cytology 2002 data

Lung FNA: Reference Diagnosis Comparison(Lab reporting rates,2001)





Sclerosing Hemangioma/Pneumocytoma

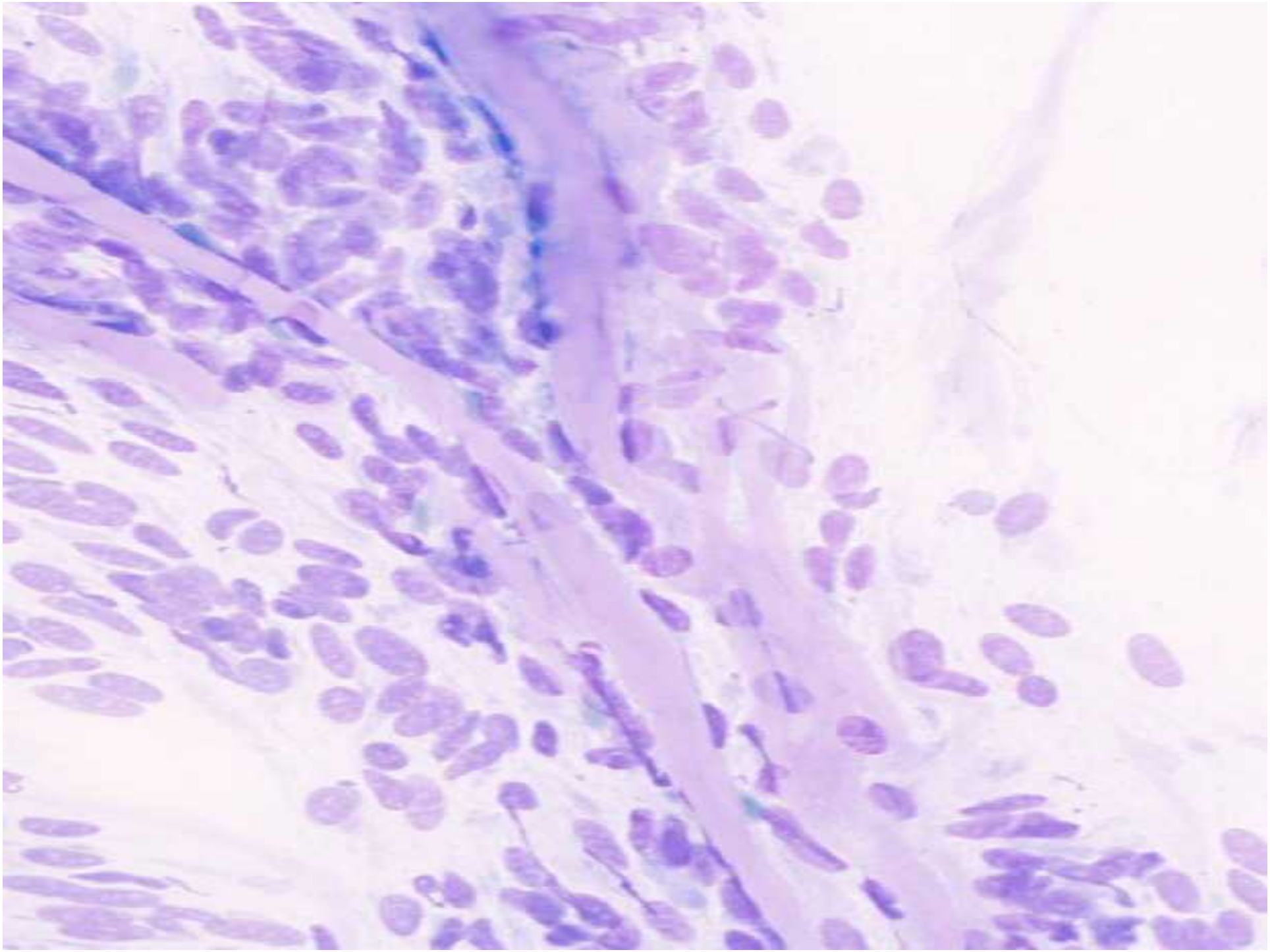
- Age full spectrum, early childhood-old
- Female preponderance, 5:1
- Incidentalomas on films, usually <3cms, well circumscribed peripheral lung lesions
- 4 basic patterns histologically- papillary, sclerotic, solid, angiomatoid
- Two basic cell types. Surface and round cells

Sclerosing Hemangioma/Pneumocytoma

- DD Well differentiated ACA. TRAP on FNA!
- TTF1 and Keratin positive too!
- Mesothelial markers negative.
- Very important to correlate clinical and radiographic findings with the cytology as these are benign/very rarely borderline lesions

Case

55 yr old male with large pleural based right lung mass. FNA and core needle biopsy performed.



Differential Diagnosis of Spindle Cell Neoplasms of Pleura & Lung

	AE1/3	CD31	CD34
Solitary FT	-	-	+
Sarc CA	+	-	-
MMeso	+	-	-
Melanoma-	-	-	
Atyp Carc	+	-	-
Sarcoma	-	+/-	-

And now **STAT 6**!!!