AN APPROACH TO
LYMPHADENOPATHY

Professor Colleen Wright
National Health Laboratory Services, Port Elizabeth
Nelson Mandela Metropolitan University, Port Elizabeth
Stellenbosch University, Cape Town
CAUSES OF LYMPHADENOPATHY

REACTIVE HYPERPLASIA
  Infective
  Autoimmune (e.g. SLE)
  Drug reactions

SPECIFIC INFECTIONS
  Viral (e.g. CMV)
  Bacterial (e.g. TB)
  Parasitic (e.g. Toxoplasmosis)
  Fungal (e.g. Cryptococcus)

NEOPLASTIC INFILTRATIONS
  Primary lymphoma (e.g. HL or NHL)
  Metastatic tumour
    Known primary
    Unknown primary
INDICATIONS FOR INTERVENTION

Persistent LAD, not responding to appropriate antibiotic therapy
Thorough examination of patient to rule out a local cause
Good history, travel, TB contacts etc.
PERSISTENT CERVICAL LYMPHADENOPATHY IN CHILDREN IN AN ENDEMIC AREA

Western Cape study

177 children tertiary referral with persistent LAD

Visible local cause 63.8%

No visible local cause

TB in 64.8%

TB in 96.9% if node mass > 2cm

Marais et al, Pediatr Infect Dis J. 2006
SIGNIFICANT PATHOLOGY

Factors related to

Individual PATIENT – age, immune status
Specific LYMPH NODES(S)
    size, site, single, mobile, matted
Specific ENVIRONMENT
INDICATIONS FOR FNAB

Neoplasm vs. reactive / inflammatory lesion
Neoplasm – benign vs. malignant
Inflammatory – aetiology
Scarce resources
On site diagnosis
  Clinical emergencies
  Patient management
CONTRAINDICATIONS

Seriously impaired lung function  
Stridor  
Uncooperative patient
COMPLICATIONS

Hematoma, hemorrhage
Vasovagal reaction, seizures
Transient nerve paresis
Tumour necrosis
Local infection
Pneumothorax
Seeding of needle tract ???
ADVANTAGES OF FNAB

Patient advantages

No hospitalisation - outpatient procedure
No sutures or scars
Minimal pain (avoid muscle)
Less morbidity
Inexpensive
Quick procedure (average less than 10 min)
Clinician advantages

Outpatient procedure
No scarring to interfere with subsequent imaging
No seeding of tumour to interfere with surgical planes
Ancillary material available for microbiology etc.
Rapid results
Minimal infrastructure required
Health care system advantages

- Optimal use of scarce resources and funds
- Triage of patients at primary and regional level
- Improved turnaround time
- Improved patient compliance
<table>
<thead>
<tr>
<th>Suitable for small lesions (1x1cm)</th>
<th>Yes</th>
<th>No</th>
<th>Yes</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire mass sampled</td>
<td>Yes, if excision</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Complications</td>
<td>Risk of anaesthesia, hospitalization, sinus formation, infection</td>
<td>Sinus formation, infection</td>
<td>Rare</td>
<td>Extremely rare</td>
</tr>
<tr>
<td>Cost</td>
<td>Hospitalization, theatre time</td>
<td>High cost of needle</td>
<td>Minimal</td>
<td>Minimal</td>
</tr>
<tr>
<td>Hospitalisation</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Anaesthetic required</td>
<td>General</td>
<td>Local</td>
<td>Local</td>
<td>None</td>
</tr>
<tr>
<td>Time for entire procedure</td>
<td>1-2 days</td>
<td>30 minutes</td>
<td>30 minutes</td>
<td>10 minutes</td>
</tr>
<tr>
<td>Tissue diagnosis</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Microscopy for organism</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Culture</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Time for initial result</td>
<td>1-2 days</td>
<td>1-2 days</td>
<td>12-24 hours (Possible in &lt;1 hr.)</td>
<td>12-24 hours (Possible in &lt;1 hr.)</td>
</tr>
</tbody>
</table>

Wright et al, Int J Tuberc Lung Dis 2009
ANCILLARY STUDIES

Flow Cytometry
Immunocytochemistry
PCR / ISH
Electron microscopy
Cell culture – chromosome analysis
Culture
Mycobacteria – MGIT, XPERT
Fungal, bacteria – Sterile saline
FNA BIOPSY IN LYMPHOMA

Primary diagnosis

Secondary diagnosis
  Staging
  Recurrence
  Transformation
  Diagnosis of infections

Tertiary diagnosis
  Special studies
  Monitor therapy
FNA abdominal lymph node under sonar guidance
2 year old male who presented with abdominal swelling and pain
CT scan showed para aortic lymphadenopathy and a mass involving the caecum
## IMMUNOPHENOTYPING

<table>
<thead>
<tr>
<th>SIZE OF CELLS</th>
<th>Intermediate</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD3</td>
<td>12.6%</td>
</tr>
<tr>
<td>CD10</td>
<td>78.9%</td>
</tr>
<tr>
<td>CD19</td>
<td>88.2%</td>
</tr>
<tr>
<td>CD20</td>
<td>84.7%</td>
</tr>
<tr>
<td>Kappa</td>
<td>0.5%</td>
</tr>
<tr>
<td>Lambda</td>
<td>82.9%</td>
</tr>
<tr>
<td>Ki67</td>
<td>95%</td>
</tr>
</tbody>
</table>

### COMMENT

Coexpression of CD19 and CD10

*t (8;14) translocation,

**BURKITT’S LYMPHOMA**
## NON-HODGKINS LYMPHOMA

<table>
<thead>
<tr>
<th></th>
<th>LYMPHOBLASTIC</th>
<th>BURKITT’S</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Nucleus</strong></td>
<td>Round/convoluted</td>
<td>Smooth/notched</td>
</tr>
<tr>
<td><strong>Chromatin</strong></td>
<td>Powdery</td>
<td>Granular</td>
</tr>
<tr>
<td><strong>Nucleoli</strong></td>
<td>Inconspicuous</td>
<td>Multiple</td>
</tr>
<tr>
<td><strong>Cytoplasm</strong></td>
<td>Very scant, blue</td>
<td>Scant, dark blue</td>
</tr>
<tr>
<td><strong>Vacuoles</strong></td>
<td>No</td>
<td>Numerous, tiny, lipid</td>
</tr>
<tr>
<td><strong>Tingible body</strong></td>
<td>Present</td>
<td>Numerous</td>
</tr>
<tr>
<td><strong>macrophages</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
FLOW CYTOMETRY

Antibodies attached to fluorescein label
Cells in fluid medium flow in single file past a laser light source
Separate needle pass in RPMI medium
2-3 million cells for basic panel
Less subjective,
B cell NHL
FLOW CYTOMETRY

B-cell Non Hodgkin's Lymphoma

- Clonality
- Lineage
- Subtype
- Grade

Monitor recurrence
FLOW CYTOMETRY

“Limitations”

Hodgkin’s Lymphoma
T cell Non Hodgkin’s Lymphoma, variants
T cell rich B cell Lymphoma
47 year old male
Long history smoking
3cm lymph node right neck
Present 3 months
Not responding to antibiotic therapy
Weight loss, cough
Chest X ray ? mediastinal nodes
? TB ? malignancy
HODGKIN’S LYMPHOMA

Background small T lymphocytes, plasma cells, lymphocytes, histiocytes
Reed – Sternberg cells and variants
   Large, pale chromatin, prominent eosinophilic nucleolus
   Pale basophilic cytoplasm
   Naked nuclei (ghost cells)
R/S cells CD45, 3, 20, EMA –
   CD 15, 30, PAX 5+
10-30% children with pulmonary TB have extra thoracic manifestations of disease
In endemic areas, TB lymphadenitis is the commonest of these (up to 50%)

TB lymphadenitis is the most common (22-48%) cause of persistent cervical LAD in endemic areas

Children may contribute up to 40% of the case load in TB endemic areas and if 5-10% of these have peripheral lymphadenopathy, FNAB may be an invaluable diagnostic aid

M tuberculosis
Mycobacterial Transport Medium for Routine Culture of FNAB

Compared mycobacterial yield and time to positive culture following bedside culture into standard MGIT tubes vs. inoculation into an inexpensive “in –house” liquid transport medium followed by immediate and delayed laboratory inoculation into MGIT tubes in 142 pairs FNAB.

Results were concordant in 94.7% cases and there was no significant difference in time to positive culture between the bedside and laboratory inoculation tubes (16.2 days S.D. 0.87 versus 17.1 days S.D. 0.85).

Wright et al Arch Dis Child 2010
DIAGNOSING MYCOBACTERIAL LYMPHADENITIS IN CHILDREN USING FNAB

Prospective study Western Cape children under 13 years
235 aspirates
35 no mycobacterial culture submitted
25 of 200 aspirates inadequate (12%)
175 aspirates entered into study
<table>
<thead>
<tr>
<th></th>
<th>CYTOLOGY</th>
<th>FLUOR</th>
<th>ZN</th>
<th>CULTURE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SENS</td>
<td>78%</td>
<td>67%</td>
<td>62%</td>
<td>75%</td>
</tr>
<tr>
<td>SPEC</td>
<td>91%</td>
<td>97%</td>
<td>97%</td>
<td>100%</td>
</tr>
<tr>
<td>PPV</td>
<td>93%</td>
<td>97%</td>
<td>97%</td>
<td>100%</td>
</tr>
<tr>
<td>NPV</td>
<td>73%</td>
<td>66%</td>
<td>63%</td>
<td>72%</td>
</tr>
<tr>
<td>EFF</td>
<td>83%</td>
<td>79%</td>
<td>76%</td>
<td>84%</td>
</tr>
</tbody>
</table>
XPERT® MTB/RIF

48/50 patients referred for FNAB at Tygerberg Hospital, South Africa, mycobacterial lymphadenitis. Positive cytomorphology with direct visualization of the organism and/or positive tuberculosis culture served as the reference standard.

Lighthelm, L et al JCM 2011
RESULTS

30 (62.5%) were diagnosed with tuberculosis (TB).

Xpert® MTB/RIF identified 29 of these cases.

Sensitivity 96.7% (29/30)

Specificity 88.9% (16/18) 6/6 (100%) of the smear negative culture positive cases.

Xpert® MTB/RIF correctly identified rifampin resistance in 1/2 cases

Lighthelm, L et al JCM 2011
XPERT® MTB/RIF CHILDREN

Prospective hospital-based study

Tygerberg hospital, Western Cape and Dora Nginza hospital, Eastern Cape, South Africa

110 children and 38 (35%) cases were excluded:

- Sensitivity: 80%
- Specificity: 93.8%
- PPV: 94.1%
- NPV: 78.9%

Coetze, L et al submitted for publication 2013
IMMUNOCYTOCHEMISTRY

Smears
Commercial spray fixative/alcohol fixation
Slides may be divided unless automated
Technique differs from IHC
Papanicolaou stained, destained

Diagnostic material confirmed prior to ICC
No prior selection of cases required
Archival material utilised
# IMMUNOCYTOCHEMISTRY PROFILE FOR TUMOUR IN A CERVICAL LYMPH NODE

<table>
<thead>
<tr>
<th></th>
<th>CK7</th>
<th>CK20</th>
<th>Pan keratin</th>
<th>CD45</th>
<th>S100</th>
<th>TTF1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melanoma</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
</tr>
<tr>
<td>NHL</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Breast carcinoma</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bronchogenic carcinoma</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Gastric carcinoma</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nasopharyngeal carcinoma</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+/-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Wright, CA  Fine needle aspiration biopsy of lymph nodes CME 2012*
### COMMON SITE OF PRIMARY TUMOURS IN LYMPH NODE METASTASES

<table>
<thead>
<tr>
<th>Node Type</th>
<th>Tumours</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inguinal nodes</strong></td>
<td>Melanoma, Anal carcinoma</td>
</tr>
<tr>
<td><strong>Axillary nodes</strong></td>
<td>Breast carcinoma, Lung carcinoma – small cell and non-small cell</td>
</tr>
<tr>
<td><strong>Cervical nodes</strong></td>
<td>Lung carcinoma – small cell and non-small cell, Melanoma, Squamous carcinoma of the oropharynx, Nasopharyngeal carcinoma</td>
</tr>
<tr>
<td><strong>Submandibular nodes</strong></td>
<td>Squamous carcinoma of the oral cavity</td>
</tr>
<tr>
<td><strong>Supraclavicular nodes</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Right</strong></td>
<td>Oesophageal carcinoma, Lung carcinoma - small cell and non-small cell</td>
</tr>
<tr>
<td></td>
<td>Breast carcinoma</td>
</tr>
<tr>
<td><strong>Left</strong></td>
<td>Gastric carcinoma (Virchow’s node), Breast carcinoma, Lung carcinoma - small cell and non-small cell</td>
</tr>
</tbody>
</table>
42 year old female, breast carcinoma 5 years previously. Mastectomy and chemotherapy. Cervical lymph node and solitary lung mass
Metastatic breast carcinoma
66 year old male chronic cough. Previously treated for TB. Now presented with cervical lymph nodes
Metastatic squamous carcinoma
Chromogranin

Metastatic small cell carcinoma
FNA IN 290 PAED ONCOLOGY PATIENTS IN MULTICENTRE SA STUDY

3 Academic oncology centres
Lymph node aspirates 100/290
Benign 49
TB 28
Reactive node 20
Abscess 1
Malignant 51
NHL 39
Burkitts 16
Other NHL 23
Hodgkin's 22
<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>96.9%</td>
</tr>
<tr>
<td>Specificity</td>
<td>97.0%</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>99.0%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>90.1%</td>
</tr>
<tr>
<td>Diagnostic accuracy</td>
<td></td>
</tr>
<tr>
<td>Malignancy</td>
<td>96.7%</td>
</tr>
<tr>
<td>Specific subtype</td>
<td>75.7%</td>
</tr>
</tbody>
</table>

Razack R. et al. Diag Cytopathology 2012
FNA TECHNIQUE

No local anaesthetic
22 gauge needle (or smaller)
10cc syringe
Minimum of 2 needle passes
Ground glass slides, frosted ends
2 smears/needle pass
   1 air-dried for MGG stain
   1 spray/ alcohol fixed for Papanicolaou stain
   Spray/fix within 10 sec