Approach to fever with lymphadenopathy

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Learning Objectives

- Knowledge of nodal distribution and anatomic drainage
- Provide an approach to the patient with peripheral lymphadenopathy with case scenarios
- Be able to differentiate between benign and serious illness
- Present a substantial differential diagnosis
- Indications for nodal biopsy
Drainage of LN

Node group, number

Supraclavicular (2-4)
Deltopleural (1-2)
Axillary (20-30)
Epitrochlear (1-2)
Inguinal (12-20)
Popliteal (6-7)

Drainage

Right side: Mediastinum, lungs
Left side: Abdomen
Arm
Arm, breast, thorax, neck
Medial side of arm below elbow
Lower extremity, genitalia, buttock, and abdominal wall below umbilicus
Lower leg
Infiltration of inflammatory cells

benign lymphocytes and macrophages in response to antigens

In situ proliferation of malignant lymphocytes or macrophages

Infiltration by metastatic malignant cells
3/4 presents with localized
1/4 present with generalized
Peripheral lymphadenopathy

- Primary or secondary manifestation of 100 illnesses
- Most cases benign, self limited illness
- The CHALLENGE is to decide if it is representative of a serious illness...
Case 1

- 25 yr male school teacher presents to you with right sided cervical lymphadenopathy - 1 week
- Nil other localisation
- His past medical history is significant for hypertension and dyslipidemia.
On physical exam 2cm anterior cervical lymph node which is firm, non-tender and mobile.

ENT exam is unremarkable.

No skin lesions are evident.

No other palpable lymphnodes
How should you proceed with this patient?

Have your patient follow up for annual physical next year.

Proceed to fine needle aspiration.

Check a CXR and CBC.

Have patient follow up in 3-4 weeks.
Epidemiology

- 925 biopsy.
- Age <30 79% benign 15% lymphomatous 6% carcinomas
- Age >50 40% benign 16% lymphomatous 44% carcinomas
- Age 30-50 indeterminate values

How should you proceed with this patient?

A. Location and duration typical for viral etiology. Have your patient follow up for annual physical next year.
B. Proceed to fine needle aspiration.
C. Check a CXR and CBC.
D. Have patient follow up in 3-4 weeks.
- It has been reported in general practice, less than one percent of patients with LAP have malignancy.
- Prevalence of malignancy is 0.4% in patients under 40 years and 4% in those over 40 years of age in the primary care setting.
- Prevalence rises to 17% in referral centre and soars to 40-60% in highly suspicious patients.
CASE 2

- 23 year girl, Puducherry
- h/o fever low grade last 15 days,
- h/o neck swelling for 1wk
- No h/o weight loss, loss of appetite
- No h/o cough
- No h/o travel
- PMH / Family / Personal history- non contributory
EXAM –

- B/L Cervical LN, erythematous rash,
- No hepatosplenomegaly
Labs –

- Hb - 8.2, Platelet - 1.1 lakh
- WBC - 4500 (N-35 %,L-60 %,M-5 %)
- LFT - S.bil -1.2, ALT- 124, ALP-156, GGTP-56
- Chest X-ray – normal
- Usg Abd - normal
What next

A. Get the FNAC / biopsy done
B. Ask for PET CT scan
C. Review your history / exam
D. Refer to ID specialist / oncologist
E. Start on antibiotics
Fever with regional lymphadenopathy
1) **Suppurative lymphadenitis** -
   Staphylococcus aureus
   Streptococcus
   Anerobes (oral)

2) **Non suppurative lymphadenitis** -
   Tuberculosis
   Toxoplasmosis
   Cat-scratch
   Kawasaki’s disease
   Kikuchi’s disease
   Malignant, metastatic, etc
This case

- FNAC – histiocytic necrotising picture
Necrosis

- Granulomas & caseation necrosis—MTB, NTM
- Necrotizing granulomas—cat scratch disease, yersinia, tularemia
- Necrotizing non granulomatous—kikuchi’s disease, SLE, kawasaki’s disease
Kikuchi disease

- uncommon, idiopathic, self-limited cause of lymphadenitis.
- Cervical lymphadenopathy, with or without systemic signs and symptoms.
- Clinically and histologically, the disease can be mistaken for lymphoma or SLE

- No specific cure. NSAIDS, Steroids
Case 3

- 18 male, h/o fever 7 days, no weight loss, no systemic localisation, no joint pain.
- He has cat, recently delivered two kittens
- k/c seizure disorder on phenytoin since last 5 yrs
- **On exam** has generalised LN, hepatosplenomegaly

- **Labs** mild thrombocytopenia, lymphocytosis with atypical lymphocyte predominance & mild hepatitis

  **D/D**-
  
  A. Tuberculosis  
  B. Lymphoma  
  C. SLE  
  D. Drugs  
  E. Mononucleosis syndrome
Algorithm to evaluate Lymphadenopathy

Attention to history and physical exam
Confirmatory testing
Environmental Exposures

- Cat Exposure - Cat-scratch disease, Toxo
- Under-cooked meat - Toxo
- Tick-Bite - Lyme’s Disease Tularemia
- Recent Blood transfusion - CMV
- High-Risk Sexual Behavior - HIV, syphilis, HSV,
  Hep B, CMV
- IVDU - HIV, Hep B, Hep C
Occupational Exposures
Travel History

Where you stand depends on where you sit”
### Epidemiological clues

<table>
<thead>
<tr>
<th>Occupational</th>
<th>Tularemia</th>
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<tbody>
<tr>
<td>Hunters, trappers</td>
<td>Erysipeloid</td>
</tr>
<tr>
<td>Fishermen, fishmongers, slaughterhouse workers</td>
<td>Coccidioidomycosis</td>
</tr>
<tr>
<td>Travel-related</td>
<td>Bubonic plague</td>
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<tr>
<td>Arizona, southern California, New Mexico, western Texas</td>
<td>Histoplasmosis</td>
</tr>
<tr>
<td>Southwestern United States</td>
<td>Scrub typhus</td>
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<tr>
<td>Southeastern or central United States</td>
<td>African trypanosomiasis (sleeping sickness)</td>
</tr>
<tr>
<td>Southeast Asia, India, northern Australia</td>
<td>American trypanosomiasis (Chagas' disease)</td>
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<tr>
<td>Central or west Africa</td>
<td>Kala-azar (leishmaniasis)</td>
</tr>
<tr>
<td>Central or South America</td>
<td></td>
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<tr>
<td>East Africa, Mediterranean, China, Latin America</td>
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Medications which can cause LN

- Phenytoin, carbapazepine
- Atenolol, Captopril, Hydralazine
- PCN, Cephalosporins, Sulfonamides

assoc with “serum-sickness” allergic reaction marked by fevers, rash, and arthralgias

- Allopurinol

usually assoc with skin eruptions (exfoliative dermatitis, TEN) or systemic febrile illness

- Gold, quinidine, pyrimethamine, sulindac, primidone
This patient

- Fever, Gen LN, hepatosplenomegaly
- Lymphocytosis, atypical lymphocyte, Generalized lymphadenopathy

Mononucleosis syndrome
Mononucleosis Syndrome

- **Symptoms-**
  - sore throat, fever, fatigue, malaise, pharyngeal inflammation,
- **Signs-**
  - lymphadenopathy, splenomegaly, hepatitis,
- **D/D–**
  - EBV, CMV, Toxoplasmosis, Acute seroconversion syndrome (HIV)
• Suspect if lymphocytosis with atypical lymphocyte (>50% lymphocyte, >10% atypical lymphocyte)  
• Serologies-
  CMV, EBV, VCA IgM, Toxo IgM
CASE 4

- 10 year old; Male
- Swelling in the neck 5 months
- Fever for one month
- Weight: 15 Kg; Height: 113 cms
- Physical Exam – Multiple lymph nodes in the neck; vertical and horizontal; non tender; mobile;
- other: unremarkable
Investigations

- Had a routine CXR
- Blood: WBC: 7,000/cmm; N: 72%; L: 28%; Hb: 8.4gm%.

Mediastinal mass:
- a. Malignancy
- b. Tubercular
- c. Sarcoidosis
This case

- Nospecific- no pressure effect of mass surrounding structures
- Chronic onset with fever and loss of weight
- mass detected on CXR
- Physical findings: cervical lymphadenopathy; fever; loss of weight.
  - 50% mediastinal masses are malignant in children
What next???

- BIOPSY
What tests would you send the sample for?

- HPE
- AFB smear and culture
- Xpert MTB RIF
GeneXpert® – a Molecular Lab in a Cartridge Fully-Integrated Sample Preparation, Amplification and Detection

- Has dramatically improved the rapid diagnosis of lymph node TB
- The sensitivity and specificity of the Xpert assay is 91.5% and 70.4% respectively.

(International Journal of Mycobacteriology Volume 4, Supplement 1, March 2015, Pages 112)
### Xpert MTB/RIF: a New Pillar in Diagnosis of Extrapulmonary Tuberculosis?

Viral Vadwai, Catharina Boehme, Pamela Nabeta, Anjali Shetty, David Alland, and Camilla Rodrigues*

<table>
<thead>
<tr>
<th>Specimen</th>
<th>Xpert Sensitivity</th>
<th>Xpert Specificity</th>
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<tbody>
<tr>
<td></td>
<td>All C+</td>
<td>S-C+</td>
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<tr>
<td>Biopsies</td>
<td>54/70 (77)</td>
<td>21/34 (62)</td>
</tr>
<tr>
<td>Pus / Abscess</td>
<td>54/56 (96)</td>
<td>8/9 (89)</td>
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<tr>
<td>Body Fluids</td>
<td>16/21 (76)</td>
<td>8/13 (62)</td>
</tr>
<tr>
<td>CSF</td>
<td>1/3 (33)</td>
<td>1/3 (33)</td>
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AFB smear and cultures positive
This case

- Importance of tissue diagnosis
- Cultures are crucial
What’s appropriate??
Fine Needle Aspirate

- Convenient, less invasive, quicker turn-around time
- Discordance of 17% between FNA and BX
Examples of appropriate patient to refer on to biopsy

- Solitary hard cervical nodule in older patient
- Supraclavicular lymphadenopathy
- Generalized firm/rubbery lymphadenopathy with systemic symptoms
Rules for Excisional Biopsy

- Use the largest/most abnormal node palpable.
- Avoid previously irradiated areas if possible.
- Supraclavicular > cervical > axillary >> inguinal
- Always ask for cultures
Yes and No No’s in lymphadeopathy
Considerations for histological diagnosis:

- Lymphoma suspects - excisional lymph node biopsies are preferred,
- If suspicion for an underlying malignancy is high, an unrevealing lymph node biopsy should be considered non-diagnostic rather than negative for malignancy, and further work-up should be pursued.
Atypical lymphoid hyperplasia should be considered non-diagnostic rather than negative for a malignancy,

- Patients should be carefully followed and an additional lymph node biopsy strongly considered
No-No’s of LN

- DO NOT use glucocorticoids unless LN is life-threatening or systemic illness dictates
  - eg. SLE flare, airway obstruction, cord compromise, SVC syndrome
    - a. Steroids can obscure some diagnoses (lymphomatous disorders)
  - b. Steroids and delay healing or activate indolent infections
- Inguinal node biopsy should be avoided, since the diagnostic yield at this site is often low
Conclusions

- Generalized LN should always prompt further clinical evaluation
- Repeated examination helps
- Most important is detail & elaborate history
- Planning BIOPSY/ FNAC in time is important
- Cultures are crucial
Thank You!