Pediatric Cervical Lymphadenopathy

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Epidemiology

- Larsson et al. 38-45% of normal children have palpable cervical lymphadenopathy
- Park et al. 90% of children aged 4-8 have lymphadenopathy
- These masses can be mistaken for other local and systemic processes
  - Congenital Masses
  - Malignancies
  - Local presentation of systemic disease
- Found by parents and caregivers and demand workup
Objectives

- Describe important History and Physical findings including workup of LAD
- Discuss pathogens responsible for acute vs subacute/chronic lymphadenitis
- Review current literature on the common causes and management of lymphadenopathy
- Review current literature on the use of ultrasound and biopsy to aid in diagnosis
- Summarize a plan for diagnosis and treatment based on evidence in the literature
Definitions

- Pathologic Lymph Node
  - >2cm in children is considered abnormal
- Acute Lymphadenopathy
  - < 2 weeks duration
- Subacute Lymphadenopathy
  - 2-6 weeks duration
- Chronic Lymphadenopathy
  - > 6 weeks duration
Pathophysiology of Lymphadenopathy

- Initial Infection
  - URI
  - Pharyngitis
  - Otitis Media
  - Odontogenic infection
- Afferent Lymphatic drainage
  - Organisms are captured by Macrophages and Dendritic cells
  - Presented on MHC molecules
- Presentation to T cells
  - Proliferation of clonal cells
  - Release of cytokines leading to chemotaxis
- Activation of B cells
  - Immunoglobulin release
  - Continued proliferation of immune response
Results of the Immune Response

- Cellular Hyperplasia
- Leukocyte Infiltration
- Tissue Edema
- Vasodilation and Capillary Leak
- Tenderness due to capsule distension
History

- OLDCARTS
- Fever, malaise, anorexia, myalgias
- Pain or tenderness of node
- Sore Throat
- URI
- Toothache
- Ear pain
- Insect Bites
- Exposure to animals
- History of travel or exposure to TB
- Immunizations
- Medications
Drug Induced Lymphadenopathy

- Medications
  - Phenytoin
  - Pyrimethamine
  - Allopurinol
  - Phenylbutazone
  - Isoniazide

- Immunizations
  - Smallpox (historically)
  - Live attenuated MMR
  - DPT
  - Poliomyelitis
  - Typhoid fever

**Usually self limited and resolves with cessation of medication or with time in the case of immunization induced LAD**
Physical Exam

- **General**
  - Febrile or toxic appearing

- **Skin**
  - Cellulitis, impetigo, rash

- **HEENT**
  - Otitis, pharyngitis, teeth, and nasal cavity

- **Neck**
  - Size
  - Unilateral vs Bilateral
  - Tender vs Nontender
  - Mobile vs Fixed
  - Hard vs Soft

- **Lungs**
  - Consolidations suggesting TB

- **Abdomen**
  - Hepatosplenomegaly

- **Extremities**
  - Inguinal and Axillary adenopathy
Differential Diagnosis

- Thyroglossal duct cyst
  - Moves with tongue protrusion and is midline
- Dermoid Cyst
  - Midline and often has calcifications on plain films
- Branchial Cleft Cyst
  - Smooth and fluctuant along SCM border
- Laryngocele
  - Enlarges with valsava
- Hemangioma
  - Mass is presents after birth, rapidly grows, plateaus, and is red or bluish in color
- Cystic Hygroma
  - Transilluminates and is compressible
- Sternocleidomastoid Tumor
  - Lymphadenopathy does not present with torticollis
- Cervical Ribs
  - Bilateral, hard and immobile
- Mumps
  - Mass palpated superior to jaw line
Laboratory Workup

- CBC with Differential
- ESR
- Rapid Streptococcal screen
- Urine VMA
- LDH
- Serology
  - EBV
  - Bartonella
  - CMV
  - Toxoplasmosis
  - Syphilis
  - HIV
- PPD placement
Imaging Workup

- **CXR**
  - To look for mediastinal lymphadenopathy

- **CT/MRI**
  - To evaluate for abscess

- **Ultrasound**
  - To evaluate for or follow progress of an abscess
  - To differentiate benign from malignant

- **EKG/ECHO**
  - If suspect Kawasaki Disease

- **Biopsy**
  - FNA or Excisional
Etiology of Lymphadenopathy

- Acute Infectious
- Subacute/Chronic Infectious
- Malignancy
- Systemic disease/Non-infectious
Yaris et al. 2006
Clinical Pediatrics

- Review of 126 children with diagnosed with lymphadenopathy
- Aim was to identify clinical and laboratory findings that aided in differential diagnosis of LAD
- 22.2% had disease other than lymphadenopathy
  - Congenital neck masses, sialadenitis, etc.
- Of patients found to have LAD
  - 76.6% had benign disease
  - 23.4% had malignant disease
- Clinical + Lab findings led to 61.2% of diagnoses
- Biopsy led to the additional 38.8% of diagnoses
Lymphadenopathy Sites in decreasing order

1. Submandibular
2. Upper Cervical
3. Middle Cervical
4. Lower Cervical
5. Pre/Postauricular
6. Supraclavicular
7. Submental
8. Occipital

Lymphadenitis vs Reactive Lymphadenopathy

- Nodal size >3cm (p = 0.004)
- Localized disease (p = 0.02)

Submandibular and Superior Cervical most common site for benign disease
Yaris et al. 2006

- Risk factors for malignant disease
  - Older age ($p = 0.002$)
  - Enlargement of supraclavicular nodes ($p = 0.001$)
  - Generalized LAD ($p = 0.003$)
  - Lymph nodes larger than 3cm ($p = 0.003$)
  - Hepatosplenomegaly ($p = 0.004$)
  - Enlarged Mediastinal Nodes ($p < 0.001$)
  - High LDH levels ($p < 0.001$)

Ellison et al. 1999

- FNA of 330 supraclavicular nodes showed 55% malignancy
Conclusions

- History and physical exam alone are very important in triage of patients with lymphadenopathy
- Minimal laboratory and radiologic studies can help identify other important risk factors
- Reactive lymphadenopathy from viral and bacterial pathogens are most common
Infectious Lymphadenopathy
Viral Lymphadenitis

- Most common form of reactive lymphadenopathy
- Common virus’ involved:
  1. Adenovirus
  2. Rhinovirus
  3. Coxsackie virus A and B
  4. EBV
- Lymphadenopathy often bilateral, diffuse, nontender
- Other Signs/Symptoms are consistent with URI
- Management is expectant but they are often biopsied due to slow regression
- Nodal architecture and hilar vascularity are normal on pathologic examination
Suppurative Bacterial Lymphadenitis

- *Staphylococcus aureus* and Group A Streptococcus
- Brodsky et al. showed aerobes 67% vs anaerobes 19%
- Common history reveals recent
  - URI
  - Earache
  - Sore Throat/Toothache
  - Skin Lesions
- Management is initially with oral or IV antibiotics depending on severity of infection
- If not resolving or getting worse
  - CT with contrast and/or Ultrasound to evaluate for phlegmon/abscess/infiltrate
- FNA vs Surgical I&D vs Surgical Excision if abscess is identified
Suppurative Lymphadenitis with Overlying cellulitis
Retrospective review of 87 cases

Aim was to determine most common causes of LAD in children and management guidelines based on clinical exam with ultrasound

Bacterial Pathogens implicated 57.5%
  - 70% unilateral lymphadenopathy

Characteristics of disease
- Erythema and tenderness of overlying skin 48.3%
- Fever 24.1%
- Infiltrate, phlegmon, or abscess found in 31%

Ultrasound was used to identify 9 abnormal nodes
  - Round lymph nodes L/S access <2
  - Abnormal hilus width or abnormal vascularization pattern

With additional test were able to identify disease on 8/9 abnormal ultrasound
  - Cat scratch (2), Mononucleosis(2), Kawasaki (2), Lymphoma (1), Lymphogranuloma maligna (1).

Ultrasound is a useful adjunct to workup of lymphadenopathy
Subacute Lymphadenitis

- 2-6 weeks duration
- Usually seen and treated with antibiotics without improvement
- Parents start to worry and want to know "What is it?"
- Margalith et al. 1995
  - Atypical Mycobacteria
  - Cat Scratch disease
  - Toxoplasmosis
  - EBV and CMV less common
Retrospective review of 60 patients <18 y/o with persistent LAD and negative cultures at 48 hours.

Performed general and specific PCR amplification of surgically excised tissue or abscess contents

Surgically removed lymph nodes were also sent for permanent staining of specific organisms

Diagnostic characteristics

- Mean age of 4.7 years with slight female predominance at 53%
- Average lymph node size was 3.2 cm
- Superior cervical chain and submandibular nodes most involved

Most common Pathogens

- Mycobacteria 61.7% of cases and 73% of these were MAI
- Legionella represented 10% of cases
- Bartonella represented 10% of cases
- Unidentified etiology in 18.3% of cases
Choi et al 2009

- **Method of identification**
  - Mycobacteria
    - Stain (70%), Culture (86.5%), PCR (81%)
  - Bartonella and Legionella
    - PCR (100%), Culture and Gram stain (0%)

- **Results of surgical therapy**
  - 90 surgical procedures performed on 60 patients
  - Cure rate was as follows
    - 95% for excisional lymphadenectomy
    - 58% for curettage
    - 23% for incision and drainage
Conclusions

1. Nontuberculous mycobacterial infections
   - PCR is a rapid way to diagnose causative organisms of LAD as cultures can take over 2 weeks for result
   - Surgical excision results in the highest cure rate and is therefore preferred unless the facial nerve or cosmesis are at risk.
   - Simple observation also works if nodes are not suppurative but this leads to protracted course

2. Cat Scratch Disease
   - PCR again is a rapid way to make the diagnosis since serologic studies have low sensitivity and specificity
   - Too small of sample size to determine if surgical vs antibiotics vs observation is superior treatment
   - Surgical treatment is necessary if abscess is identified as reported in 10-20% of cases

3. Legionella lymphadenitis
   - PCR provides rapid diagnostic benefits as legionella grows on special media
   - Levofloxacin/Moxifloxacin/Azithromycin +/- Rifampin
   - Incision and drainage plus antibiotics showed recurrence in 6/7 patients
   - Surgical excision is recommended but larger sample needed to detect significant difference.
Atypical Mycobacteria

- #1 cause of subacute disease
- Species involved:
  - *Mycobacterium avium-intracellulare*
  - *Mycobacterium scrofulaceum*
- Develops over weeks to months
- Lymph nodes are tender, rubbery, and may have violaceous discolored skin over the node
- Diagnosis by acid fast stain and culture of material from lymph node (FNA) which can take weeks
- Untreated disease may lead to sinus tract and cutaneous drainage for up to 12 months
- Treatment historically has been surgical excision of involved lymph nodes

**Different from Tuberculous LAD where lymphadenopathy is a more ominous sign of disseminated disease if found in lymph nodes.**
Mycobacterial Lymphadenitis
Zeharia et al 2008
Pediatric Infectious Disease

- Retrospective review of 92 children with chronic non-TB mycobacterial cervical lymphadenitis
- Parents opted for conservative treatment
- Patients followed for at least 2 years.
- Cultures and PCR used to verify mycobacteria
- Diagnostic Characteristics
  - <4 yrs old and nodal size > 3 cm in 80% of cases
  - Unifocal lymphadenopathy in 90% of cases
  - Submandibular (50%) > Cervical (25%) > Preauricular (10%)
  - Positive PPD >10mm in 85% of cases
  - MAI and M. haemophilum isolated in 90% of cases
Outcomes

- Dominant nodes showed purulent drainage in 97% of patients for 3-8 weeks
- Total Resolution
  - 6 months in 71%
  - 9 months in 98%
  - 12 months in 100%
- No complications other than a skin colored flat scar in the area of drainage at 2 year follow up
Conclusions

- Previous randomized controlled trials have shown increased benefit of Surgery over Clarithromycin plus Rifabutin.
- Surgical Therapy Complication rates of 10-28%
  - Large incision with poor cosmetic result
  - Fistula formation and prolonged wound drainage
  - Repeat surgical procedures for recurrence
  - Secondary *S. aureus* wound infections
  - Transient or permanent facial nerve paralysis
- Therefore expectant management is recommended however a randomized study comparing surgery and observation is needed.
Cat Scratch Disease

- Species involved:
  - Bartonella Henselae
- Age <20, M>F,
- 90% have had exposure to cat bite or scratch
- Can take up to 2 weeks to develop
- Tender LAD are usually present however, fever and malaise are mild and present in <50% of patients (Twist)
- Diagnosis with serology for antibodies or PCR
- Historically management has been expectant with antibiotics reserved for rare cases with complicated courses (Windsor 2001)
- Antibiotics always given to immunocompromised patients to prevent disseminated disease

**Other less common zoonotic causes are tularemia, brucellosis, and anthracosis.
Cat Scratch Disease Herald Papule
Facial Papule with Adenopathy
Bass et al. 1998
Pediatric Infectious Disease

- Prospective Randomized Double Blinded Placebo controlled trial
- 29 patients randomized to Azithromycin x 5 days vs Placebo (14 and 15 respectively)
- Lymph node volume calculated until total lymph node volume was less than 20% original value

Results
- Azithromycin group showed 50% success rate at 30 days while placebo group showed only 7% success ($p<0.02$)
- After 30 days however the rate or degree of resolution was not significantly different between groups
Conclusions

- Antibiotic therapy is indicated to rapidly decrease node size within the first 30 days.
- Antibiotic therapy should be considered in all patients, especially those who are immunocompromised and at increased risk for disseminated disease.
- Suppurative lymphadenitis occurs in 10% of patients from previous reports, but surgical drainage is rarely necessary unless spontaneous rupture is imminent.
Toxoplasmosis

- *Toxoplasma gondii*
- Mechanism
  - Consumption of undercooked meat
  - Ingestion of oocytes from cat feces
- Symptoms
  - Malaise, fever, sore throat, myalgias
  - 90% have cervical lymphadenitis
- Diagnosis by serologic testing
- Complications include
  - myocarditis
  - pneumonitis
  - Risk of TORCH infection to fetus
- Treatment with pyrimethamine or sulfonamides
Infectious Mononucleosis

- Caused by Epstein Barr Virus
- Epidemiology
  - 50% seropositive by age 5
  - 90% seropositive by age 25
- Signs/Symptoms
  - Fever
  - Exudative pharyngitis
  - Painless generalized lymphadenopathy
  - Axillary LAD and Splenic enlargement increase likelihood
  - 50% lymphocytosis with >10% Atypical lymphocytes on peripheral smear is suggestive
- Diagnosis
  - Positive monospot test
  - Serum heterophile Antibody definitive
    - 60% positive at 2 weeks while 90% are positive at 1 month
- Treatment is expectant and supportive
  - Tonsillar hypertrophy can become bad enough to produce airway obstruction and you may need to place nasopharyngeal tube and start high dose steroids
  - Do not give amoxicillin as patients will develop an iatrogenic rash in 80% of patients.
  - No sports for 8 weeks to prevent splenic injury and rupture
Infectious Mononucleosis Findings
Maculopapular EBV Rash with Amoxicillin
Chronic Lymphadenitis

- >6 weeks
- Subacute pathogens frequently implicated
- Risk of Malignancy increased
  1. Neuroblastoma
  2. Rhabdomyosarcoma
  3. Leukemia/Lymphoma
- Supraclavicular (Ellison 1999) and posterior triangle adenopathy (Putney 1970) are at increased risk for malignancy.
- Almost all patients receive biopsy at this point
- Excisional biopsy often needed to obtain enough tissue for diagnosis
- Management is usually a referral a medical oncologist given the age group and most common cancers identified
Non-Infectious Lymphadenopathy
Kawasaki Disease

- Lymphomucocutaneous Disease
- Five Characteristics of Disease (4/5 for diagnosis)
  - Fever >5 days
  - Cervical lymphadenopathy (usually unilateral)
  - Erythema and edema of palms and soles with desquamation of skin
  - Nonpurulent Bilateral Conjunctivitis
  - Strawberry Tongue
- Complications
  - Coronary artery aneurysms
  - Coronary artery thromboses
  - Myocardial infarction
- Treatment
  - IVIG and Aspirin

**Be sure to get Echo and EKG is Kawasaki disease is suspected**
Systemic Manifestations of Kawasaki Disease
Kikuchi-Fujimoto disease

- Also known as necrotizing lymphadenitis
- Benign condition
- Affects young Japanese girls
- Associated Signs and Symptoms
  - Fever
  - Nausea
  - Weight loss
  - Night Sweats
  - Arthralgias
  - Hepatosplenomegaly
- Thought to have viral or autoimmune etiology
- The majority spontaneously regress within 6 months, however some patients have recurrences
Massive, painless, bilateral cervical adenopathy
Benign condition
Generalized proliferation of sinusoidal histiocytes
First decade of life with 2M:1F
Associated signs and symptoms
- Fever
- Neutrophilic leukocytosis
- Polyclonal hypergammaglobulinemia
Most patients will get a biopsy given the large adenopathy
Characteristic biopsy showing sinus expansion with histiocytes and phagocytosed lymphocytes (Foucar 1990)
Treatment is supportive and most patients have spontaneous regression
Rosai-Dorfman Lymphadenopathy
Langerhans Cell Histiocytosis

- Eosinophilic Granuloma
  - Solitary bone, skin, lung, or stomach lesions
- Hands-Schuller-Christian Disease
  - Diabetes Insipidus, Exophthalmos, Lytic bone lesions
- Letterer-Siwe disease
  - Life threatening multisystem disorder
  - 50% 5 year survival
- 1/3 of patients will have background LAD
- Histopathology shows normal lymph node architecture but increase sinusoidal Langerhans’ cells, macrophages, and eosinophils
- Treatment with topical steroids, oral steroids, and even chemoradiation therapy
Lytic Bone Lesion of Histiocytosis
Role of Ultrasound (Ahuja et al. 2005)

- No radiation exposure
- Good for following the progress of an abscess
- Differentiate Reactive vs Malignant nodes
  - **Reactive**
    - <1 cm
    - Oval (S/L ratio <0.5cm)
    - Normal hilar vascularity
    - Low resistive index with high blood flow
  - **Malignant**
    - >1 cm
    - Round (S/L ratio >0.5cm)
    - No echogenic hilus
    - Cogaulative necrosis present
    - High resistive index with low blood flow
    - Extracapsular spread
- Sensitivity 95% and Specificity 83% for differentiating reactive vs metastatic lymph nodes
The Role of FNA

- Minimally invasive
- Low morbidity
- Not as reliable in children as in adults so you can only trust FNA if it is positive (Twist 2000)
- Chau et al. 2003
  - Evaluated FNA of 289/550 patients referred with LAD
  - Sensitivity 49% and Specificity of 97%
  - False negative rate of 45%
  - 83% of false negatives were lymphomas
The Role of Excisional Biopsy

- Still the gold standard for diagnosis
- Consider if FNA is inconclusive or if FNA is negative but your suspicion for malignancy is high
- You must excise the largest and firmest node that is palpable and must remove the node with the capsule intact (Twist 2000)
Summary

- History and Physical exam alone can be used to diagnose and direct treatment in the majority of acute lymphadenopathy cases
- Treat acute lymphadenopathy with 2 weeks of antibiotics and re-evaluate
- If you suspect abscess or patient is toxic, order CT scan and follow abscess/phlegmon with repetitive ultrasound.
- Further workup with serology, imaging, and biopsy are necessary with resistant, subacute and chronic cases
- Atypical Mycobacteria treatment
  - Surgery vs Observation
  - Each patient is different and we need a randomized trial comparing the two
- Cat Scratch Disease
  - Azithromycin is good at rapidly decreasing the size of lymphadenopathy but is not better than observation in the long term
  - Antibiotics are mandatory for severe cases and immunocompromised.
Summary cont’d

- Ultrasound is a very useful adjunct to help characterize and differentiate reactive, suppurative, and metastatic lymph nodes.
- FNA Biopsy is indicated for:
  - Supraclavicular nodes
  - Nodes larger than 3cm in size
  - Nodes present longer than 6 weeks
- Remember that excisional biopsy may be indicated if node persists and FNA is either negative or inconclusive.
References

Ahuja AT, Ying M. Sonographic evaluation of cervical lymph nodes. AJR Am J Roentgenol. 2005 May;184(5):1691-9


References