Management of Lymphadenopathy

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Introduction

- Lymphadenopathy:
  an abnormality in the size or character of lymph nodes.

“Scrofula” which is a Latin word for a glandular swelling, dates back to about 3000 years, Hippocrates of Cos (460–377 bc) "Father of Medicine", has also described two cases of scarlet fever with fever, severe sore throat, red rash, strawberry tongue and lymphadenopathy.
Introduction

- Categories of Lymphadenopathy: (MIAMI) Malignancies, Infections, Autoimmune disorders, Miscellaneous and unusual conditions, and Iatrogenic causes.

- The most concerning to the patient and physician:
  - the possibility of underlying malignancy
Objectives

- Approach to lymphadenopathy
  - Who to investigate
  - When to investigate
  - How to define risk for underlying malignancy
Lymph Nodes

- **Anatomy**
  - Collection of lymphoid cells attached to both vascular and lymphatic systems
  - Over 600 lymph nodes in the body

- **Function**
  - To provide optimal sites for the concentration of free or cell-associated antigens and recirculating lymphocytes – “sensitization of the immune response”
  - To allow contact between B-cells, T-cells and macrophages

- Lymphadenopathy - node greater than 1cm in size.
Why do lymph nodes enlarge???

- Increase in the number of benign lymphocytes and macrophages in response to the antigens.
- Infiltration of inflammatory cells in infection (lymphadenitis).
- In situ proliferation of malignant lymphocytes or macrophages.
- Infiltration by metastatic malignant cells.
- Infiltration of lymph nodes by metabolite laden macrophages (lipid storage diseases)
Epidemiology

- **Retrospective review**
- 457 children aged 2 mo - 19 yrs
- 76% benign, 24% malignant
- 61% of the benign group had an unknown etiology
- Most common benign etiologies: EBV and acute lymphadenitis
- Most common malignant: Hodgkin’s and NHL
- None in the infant group had a malignant process.

When to worry??

- Age
- Characteristics of the node
- Location of the node
- Clinical setting associated with lymphadenopathy
Age

- Children – more likely to respond to minor stimuli with lymphoid hyperplasia. Malignant rate increases with age.
- A majority of healthy children have palpable cervical, inguinal and axillary adenopathy.
- Most of them is infectious or benign in etiology.
- Lymphadenopathy that lasts less than 2 weeks or more than 1 year with no progressive size increase has a very low likelihood of being neoplastic.
- Rare Exception: low-grade Hodgkin’s/ non-Hodgkin’s lymphomas and, occasionally, chronic lymphocytic leukemia.
History

- **Duration**
  - Short (< 2 weeks) - likely to be infectious.
  - Long (> 2 weeks but < 1 year) - likely to be infectious, malignancy, autoimmune, drug reaction.
  - Very long (> 1 year) likely to be pathologic but not malignancy.

- **Identifiable cause for the lymphadenopathy?**
  - Localizing symptoms or signs to suggest infection/neoplasm/trauma at a particular site/pets.
    - URTI, pharyngitis, periodontal disease, conjunctivitis, insect bites, recent immunization etc.
History

- Constitutional symptoms: fever, fatigue, malaise with atypical lymphocytosis → **mononucleosis syndromes**.
- Significant fever, night sweats, unexplained BW loss > 10% of normal BW → “**B**” symptoms of Hodgkin’s lymphoma.
- Arthralgias, muscle weakness, unusual rash → autoimmune diseases such as RA, SLE, dermatomyositis.

Epidemiological clues

- Occupational exposures, recent travel.
- Medications – Chronic use of medications, serum-sickness syndrome.
- Family history, AIDS patient.
Drugs

- Allopurinol
- Atenolol
- Captopril
- Carbamazepine
- Gold
- Hydralazine
- Penicillins

- Phenytoin
- Primidone
- Pyrimethamine
- Quinidine
- Trimethoprim/Sulfamethoxazole
- Sulfinpyrazone
Physical Exam

- Full nodal examination – nodal characteristics
- Organomegaly.
- Localized – examine area drained by the nodes for evidence of infection, skin lesions or tumours.
- Localized/Generalized.
Superficial palpable lymph nodes.
Characteristics of the node

- Consistency – Hard/Firm vs Soft/Fluctuant
- Mobile vs Fixed
- Tender vs Painless
- Clearly demarcated/Matted
- Size

**When to worry** – 1.5-2cm in size
- Epitroclear nodes over 0.5cm; Cervical/Axillary over 1 cm and Inguinal over 1.5cm.

- Duration and Rate of Growth
**Preauricular nodes:**
- Drain scalp, skin

**Differential diagnosis:**
- Scalp infections, mycobacterial infection

**Malignancies:**
- Skin neoplasm, lymphomas, head and neck squamous cell carcinomas

**Posterior cervical nodes:**
- Drain scalp, neck, upper thoracic skin

**Differential diagnosis:**
- Same as preauricular nodes

**Supraclavicular nodes:**
- Drain gastrointestinal tract, genitourinary tract, pulmonary

**Differential diagnosis:**
- Abdominal/thoracic neoplasms, thyroid/laryngeal disease, mycobacterial/fungal infections

**Submandibular nodes:**
- Drain oral cavity

**Differential diagnosis:**
- Mononucleosis, upper respiratory viral/bacterial infection, mycobacterial infection, toxoplasma, cytomegalovirus, dental disease, rubella

**Malignancies:**
- Squamous cell carcinoma of the head and neck, lymphomas, leukemias

**Anterior cervical nodes:**
- Drain larynx, tongue, oropharynx, anterior neck

**Differential diagnosis:**
- Same as submandibular nodes

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Head and Neck Lymphadenopathy

- Infection is the most common cause.
- Acute bilateral - adenovirus, influenza, RSV; EBV and CMV
- Acute unilateral - strep or staph (40-80%)
- Most cases resolve quickly; some entities can create persistent lymphadenopathy for months. (ex. Atypical mycobacteria, cat-scratch disease, toxoplasmosis, Kawasaki’s syndrome.).

- **Supraclavicular lymphadenopathy**
  - Highest risk of malignancy – estimated as 90% in patients older than 40 years vs 25% in those younger than 40 yrs
  - Right sided node – cancer in mediastinum, lungs, esophagus
  - Left sided node (Virchow’s) – testes, ovaries, kidneys, pancreas, stomach, gallbladder or prostate
Head and Neck
Lymphadenopathy

Figure 11.1 The anatomical triangles of the neck.

Figure 11.9 The site of a branchial cyst.

Figure 11.18 The site of a cervical rib.

Figure 11.19 The sites of a thyroglossal cyst.

Figure 11.12 The site of a carotid body tumour.

Figure 11.16 The site of a sternomastoid tumour.

Figure 11.13 The site of a cystic hygroma.

Figure 11.15 The site of a pharyngeal pouch.

A scheme for the diagnosis of swellings in the neck:

1. After your examination you should be able to answer four critical questions: Is there one or more than one lump? Size? Soft or cystic? Does it move with swallowing?

2. A single lump:
   - In the anterior triangle that does not move with swallowing: Solid
     - A lymph node
     - Cystic
     - Cyst hygroma
     - Pharyngeal pouch
     - Sialoadenitis
   - In the posterior triangle that moves with swallowing: Solid
     - Branchial cleft cyst

3. Multiple lumps are invariably lymph nodes.
Supra clavicular node
Head and Neck Lymphadenopathy

Neck – supraclavicular region huge neglected swelling of lymphatic origin extending down to the chest cavity
Inguinal Lymphadenopathy

Differential diagnosis:
Benign reactive lymphadenopathy, sexually transmitted diseases, skin infections

Malignancies:
Lymphomas; squamous cell carcinoma of penis, vulva, and anus; skin neoplasms; soft tissue/Kaposi’s sarcoma

Horizontal node group
Vertical node group

These groups drain lower abdomen, external genitalia (skin), anal canal, lower ⅓ of vagina, lower extremity
Inguinal Lymphadenopathy

- It is common, with nodes enlarged up to 1 to 2 cm in diameter in many healthy children and adults, but it has of low suspicion of malignancy.

- Benign reactive lymphadenopathy and infection are the most common etiologies.

- Although some tumors, such as Hodgkin’s lymphomas, penile/ vulvar SCC, melanoma in this area, may present with inguinal lymphadenopathy, it is typical presenting finding in neither case.
Axillary Lymphadenopathy

- Most of cases are nonspecific or reactive to local injury/infection in etiology.
- Persistent lymphadenopathy is less commonly found in the axillary nodes than in the inguinal chain.
- Antecubital or epitrochlear lymphadenopathy can suggest lymphoma or melanoma of the extremity.
Inguinal Lymphadenopathy

Infradavicular nodes:
- Highly suspicious for non-Hodgkin's lymphoma

Axillary nodes:
- Drain breast, upper extremity, thoracic wall

Differential diagnosis:
- Skin infections/trauma, cat-scratch disease, tularemia, sporotrichosis, sarcoidosis, syphilis, leprosy, brucellosis, leishmaniasis

Malignancies:
- Breast adenocarcinomas, skin neoplasms, lymphomas, leukemias, soft tissue/Kaposi's sarcomas

Epitrochlear nodes:
- Drain ulnar forearm, hand

Differential diagnosis:
- Skin infections, lymphoma, and skin malignancies
BCG Adenitis

- BCG lymphadenitis refers to cases where the lymph nodes have become large enough, after vaccination, to be easily palpable and a cause of concern for the parents.

- Most of the cases appear within 6 months of the BCG.

- Ipsilateral axillary glands are involved in more than 95% of the cases, though the supraclavicular or cervical glands may occasionally be enlarged in isolation or association.

- Two forms of lymphadenitis can be recognized, non-suppurative or simple which may resolve spontaneously within a few weeks, or suppurative which is marked by the appearance of fluctuation with erythema and oedema of the overlying skin.
BCG Adenitis

- Once suppuration has occurred, the subsequent course is usually one of spontaneous perforation, discharge and sinus formation.
- Healing eventually takes place through cicatrization and closure of the sinus, the process taking several months.
- In patients with large and persistent or recurrent lymphadenopathy, possibility of underlying immunodeficiency should be investigated. Thus all infants presenting with BCG lymphadenitis should be followed up till resolution.
BCG Axillar Lymphadenitis BCG Cervical lymphadenitis
Generalized Lymphadenopathy

- Generalized lymphadenopathy: lymphadenopathy found in two or more distinct anatomic regions.
- More likely to result from serious infections, autoimmune diseases, and disseminated malignancies.
- Specific testing is usually required.
- Generalized adenopathy infrequently occurs with neoplasms, but it is occasionally seen in patients with leukemias and lymphomas, or advanced disseminated metastatic solid tumors.
Generalized Lymphadenopathy

- Malignancy – lymphoma, leukemia, Kaposi’s sarcoma, metastases
- Autoimmune – SLE, RA, Sjogren’s syndrome, Still’s disease, Dermatomyositis
- Infectious – Brucellosis, Cat-scratch disease, CMV, HIV, EBV, Rubella, Tuberculosis, Tularemia, Typhoid Fever, Syphilis, viral hepatitis, Pharyngitis
- Other – Kawasaki’s disease, sarcoidosis, amyloidosis, lipid storage diseases, hyperthyroidism, necrotizing lymphadenitis, histiocytosis X, Castlemen’s disease
Risk factors.

- Hard and painless nodes have higher suspicion of malignancy or granulomatous disease.

- Viral infection typically produces hyperplastic nodes that are bilateral, mobile, nontender, and clearly demarcated.

- Palpable supraclavicular and popliteal nodes of any size and epitrochlear nodes larger than 5mm are considered abnormal.

- Increasing size and persistence over time are of greater concern for malignancy than a specific level of nodal enlargement.
Management

- Identify underlying cause and treat as appropriate – confirmatory tests.
- Generalized adenopathy – usually has identifiable cause.
- Localized adenopathy
  - 2-3 week observation period for resolution if not high clinical suspicion for malignancy.
  - Biopsy if risk for malignancy – excisional.
Investigations.

- The evaluation of lymphadenopathy may include a number of tests as indicated by the history, physical examination, differential diagnosis, index of suspicion and the anxiety of the patient, parent and health care provider. These may include:
  - Laboratory - complete blood count with differential, erythrocyte sedimentation rate or C-reactive protein, lactate dehydrogenase, uric acid, liver function tests
  - Purified Protein Derivative skin test for Tuberculosis /cultures, PCR.
  - Viral titers
  - Other titers - Toxoplasmosis, *Bartonella henselae*
  - Chest radiograph
  - Consultation with surgery, oncology, rheumatology, infectious disease, radiology
  - Biopsy
Fine Needle Aspirate

- Convenient, less invasive, quicker turn-around time, safe.
- Most patients with a benign diagnosis on FNA biopsy do not undergo a surgical biopsy.
Indications of Biopsy

1- Persistent unexplained fever, weight loss, Night sweats.

2- Hard nodes/fixation of nodes to surrounding tissues.

3- Increase in size over base line in 2 weeks.

4- No decrease in size over 4-6 weeks.

5- No regression to normal 8-12 weeks.

or if new signs/symptoms develop.
Lymph Node Biopsy

- Once biopsy has been chosen, ideally the largest, most suspicious, and most accessible node is selected, taking into account differing diagnostic yields by site.
- Inguinal nodes offer the lowest yield, and supraclavicular nodes have the highest.
- Excisional biopsy remains the diagnostic procedure of choice.
Role of the surgeon

- **Acute suppurative lymphadenitis.**
  - Conservative, I/V Antibiotics,
  - Incision/drainage of Abscess

- **BCG Adenitis.**
  - No treatment to surgical drainage, administration of Anti T B drug or combination of drugs and surgery. Fistulated /adherent LN need surgical excision while non adherent lesions heal spontaneously without treatment.

- **Non Tuberculos Mycobactarial lymphadenitis.**
  - Surgical excision is the mainstay of treatment.
Approach to Lymphadenopathy

1. Lymphadenopathy
   - Yes
   - Significant Physical Signs or Symptoms?
     - Yes
     - Use Antibiotics
     - 2-3 Weeks
     - Node(s) Resolving
       - Observe and Follow
     - Node(s) Increase in size Not Resolving
       - Investigate
     - Node(s) Resolving
   - No
   - Observe ? Use Antibiotics

2. No
   - Reassure Family
Conclusions

- Lymphadenopathy – initial presenting symptom
- Reactive vs Malignant
  - Probability
  - History
  - Physical Exam
- Biopsy if not resolved in 3-4 weeks for low risk patients
- Biopsy all high risk patients – excisional biopsy