CancerCare Manitoba
ActionCancerManitoba

Blood Disorders Day 2018

FOR Health Professionals

Investigation of Splenomegaly & Lymphadenopathy

May 4, 2018

University of Manitoba

CancerCare Manitoba
COMMUNITY ONCOLOGY PROGRAM

Presenter Disclosure

- **Faculty / Speaker's name: Dr. Pamela Skrabek**

- **Relationships with commercial interests:**
  - **Grants/Research Support:** none
  - **Speakers Bureau/Honoraria:** none
  - **Consulting Fees:** Celgene, Bristol Myers Squibb
  - **Other:** none

Mitigating Potential Bias

- I will not be discussing pharmaceuticals

Learning Objectives

1. To be able to determine if splenomegaly is concerning
2. In a patient with splenomegaly know clinical context where Hematology referral is beneficial
3. When a patient has lymphadenopathy outline an approach to investigation and understand when to suspect lymphoma

Introduction

- Enlarged lymph nodes & splenomegaly common
- Wide differential diagnosis for both
- Clinical or diagnostic significance of a spleen that is modestly enlarged on scan but is not palpable (ie, "scanomegaly")[1] is uncertain

1. Schrier S et al. “Approach to adult with splenomegaly and other splenic disorders” UTD Topic 7134, version 58.

Spleen Function

- Immune organ
- Phagocytosis of erythrocytes
- Site of hematopoiesis
- Blood reservoir

Spleen Size

- Normal is actually hard to define
  - Varies by height, gender, race
- A palpable spleen is usually enlarged
- Ultrasound Length > 13 cm
- CT normal volume from 107 to 315 cm^3,
  - One study correlates this to maximum length of 10 cm*

Grover et al., Does this Patient Have Splenomegaly? JAMA, Nov 10, 1993 – Vol 270, No.18.
* Bezerra A et al. AJR:184, May 2005

Causes Splenomegaly

10 - 36%
- Infection – most common viral
- Autoimmune disorders
- Sarcoidosis

30%
- Hemolysis
- Hematological malignancy - Myeloproliferative neoplasms, lymphoma

- Obstructed venous blood flow - cirrhosis, portal vein thrombosis
- Hepatic disease 25-41%

1. O'Reilly RA. West J Med. 1998; 169(2):88±97. 2. O'Reilly RA. Am J Med Sci. 1996; 312(4):160±5.
3. Curovic Rotbain, Emelie et al. "Splenomegaly – Diagnostic Validity, Work-Up, and Underlying Causes." *PLoS ONE* 12.11 (2017): e0186674.

Splenomegaly Referral

Consult Service: Hematology / CCMB.

Level of Urgency:	**Reasons for Consultation:**		
☐ Emergent* (patient to be seen within < 1 hr)	☐ Clinical Question	☐ Outpatient Follow Up	☐ Education and Care
☐ Urgent (patient to be seen within < 4 hrs)	☐ Transfer of Care	☐ Mandatory	☐ Other*
☐ Non-Urgent (patient seen within 24hrs)			
* Requires Attending MD to Attending MD phone call/conversation			

Key Features Relevant to Question: 50yo. ♂ w PmHx Down Syndrome, Cardiac Surgery ToF, presenting with ↓ weight / ↓plt (64) / ↓Hgb (85) (WNL 2016). Enlarged spleen. Please R/O 1° hematologic malignancy with bone marrow bx.

FINDINGS:

Examination was performed without the benefit of IV contrast due to a high serum creatinine. This limits assessment of solid organs. Allowing for this:

Images of the lung bases demonstrate a trace right pleural effusion. Heart is enlarged.

There is minimal ascites adjacent to the liver. Spleen is enlarged measuring approximately 15.1 cm in length. No gross focal splenic lesion. The gallbladder is present. Liver, pancreas, adrenals and kidneys appear grossly unremarkable. There appears to be circumferential urinary bladder wall thickening. A small amount of free fluid is present within the pelvis. No pathologically enlarged intra-abdominal or pelvic lymph nodes by CT criteria. No gross bowel abnormalities although endoscopy is more sensitive for detection of GI pathology including malignancy..

IMPRESSION:

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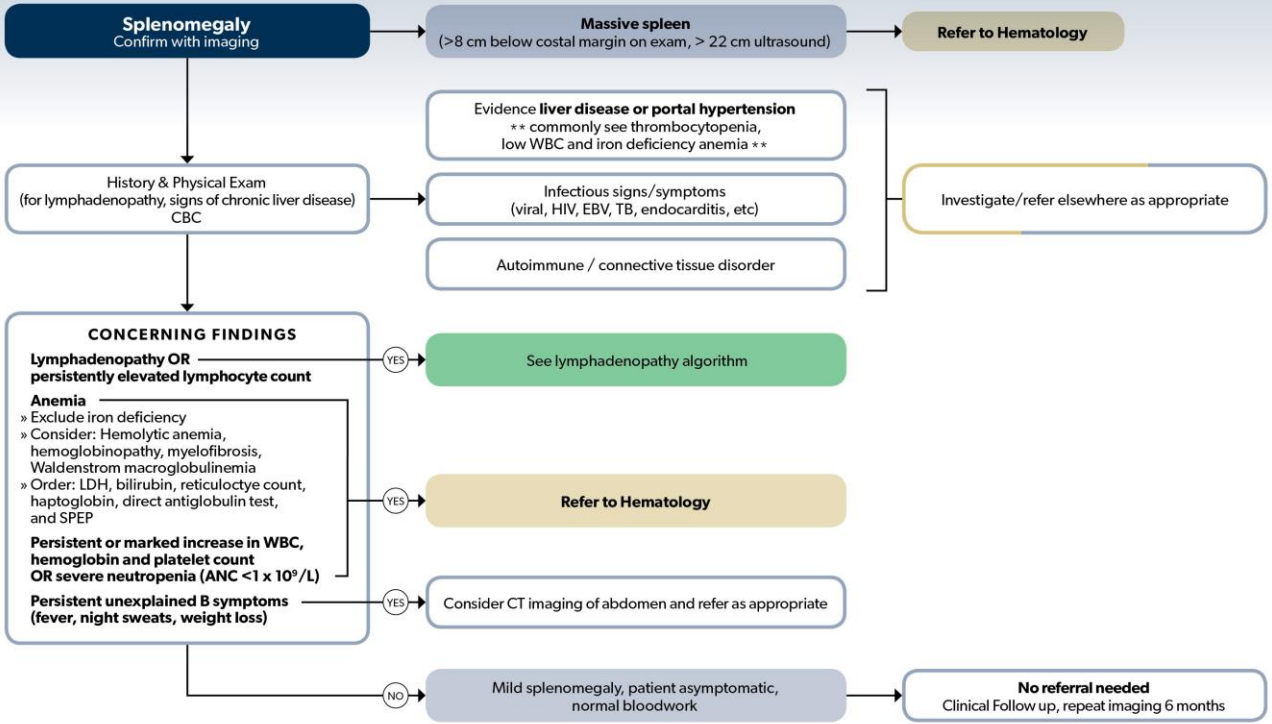
Splenomegaly

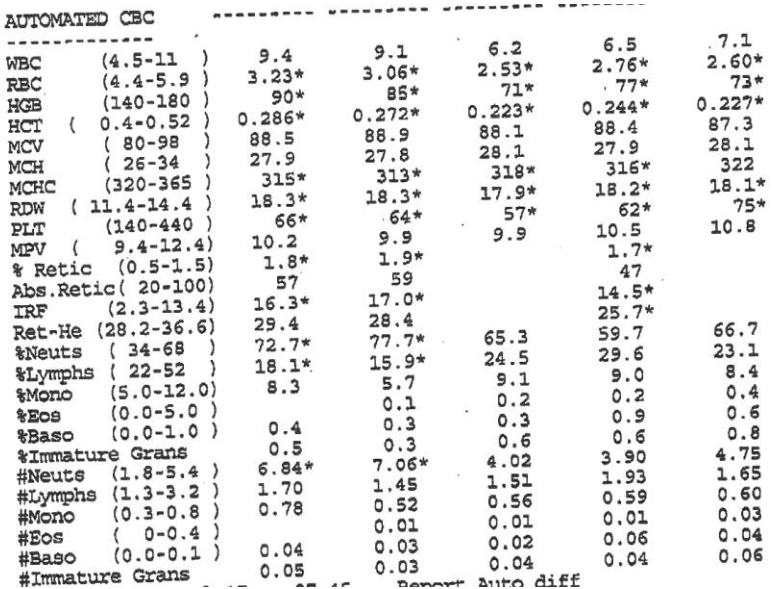


Definition Splenomegaly: Palpable, > 13 cm on ultrasound

Platelet count < 75 x 10^9/L, or WBC count < 3 x10^9/L may be less likely attributed to portal hypertension

Splenomegaly Referral

Weight loss, fatigue, ? petechiae legs, low grade fevers. Bioprosthetic pulmonlyar valve. Exam with spleen tip palpable, 1.5 cm inguinal LN, petechiae/ some large more like purpura



AUTOMATED CBC						
WBC	(4.5-11)	9.4	9.1	6.2	6.5	7.1
RBC	(4.4-5.9)	3.23*	3.06*	2.53*	2.76*	2.60*
HGB	(140-180)	90*	85*	71*	77*	73*
HCT	(0.4-0.52)	0.286*	0.272*	0.223*	0.244*	0.227*
MCV	(80-98)	88.5	88.9	88.1	88.4	87.3
MCH	(26-34)	27.9	27.8	28.1	27.9	28.1
MCHC	(320-365)	315*	313*	318*	316*	322
RDW	(11.4-14.4)	18.3*	18.3*	17.9*	18.2*	18.1*
PLT	(140-440)	66*	64*	57*	62*	75*
MPV	(9.4-12.4)	10.2	9.9	9.9	10.5	10.8
% Retic	(0.5-1.5)	1.8*	1.9*		1.7*	
Abs.Retic	(20-100)	57	59		47	
IRF	(2.3-13.4)	16.3*	17.0*		14.5*	
Ret-He	(28.2-36.6)	29.4	28.4		25.7*	
%Neuts	(34-68)	72.7*	77.7*	65.3	59.7	66.7
%Lymphs	(22-52)	18.1*	15.9*	24.5	29.6	23.1
%Mono	(5.0-12.0)	8.3	5.7	9.1	9.0	8.4
%Eos	(0.0-5.0)		0.1	0.2	0.2	0.4
%Baso	(0.0-1.0)	0.4	0.3	0.3	0.9	0.6
%Immature Grans		0.5	0.3	0.6	0.6	0.8
#Neuts	(1.8-5.4)	6.84*	7.06*	4.02	3.90	4.75
#Lymphs	(1.3-3.2)	1.70	1.45	1.51	1.93	1.65
#Mono	(0.3-0.8)	0.78	0.52	0.56	0.59	0.60
#Eos	(0-0.4)		0.01	0.01	0.01	0.03
#Baso	(0.0-0.1)	0.04	0.03	0.02	0.06	0.04
#Immature Grans		0.05	0.03	0.04	0.04	0.06

Report Auto diff

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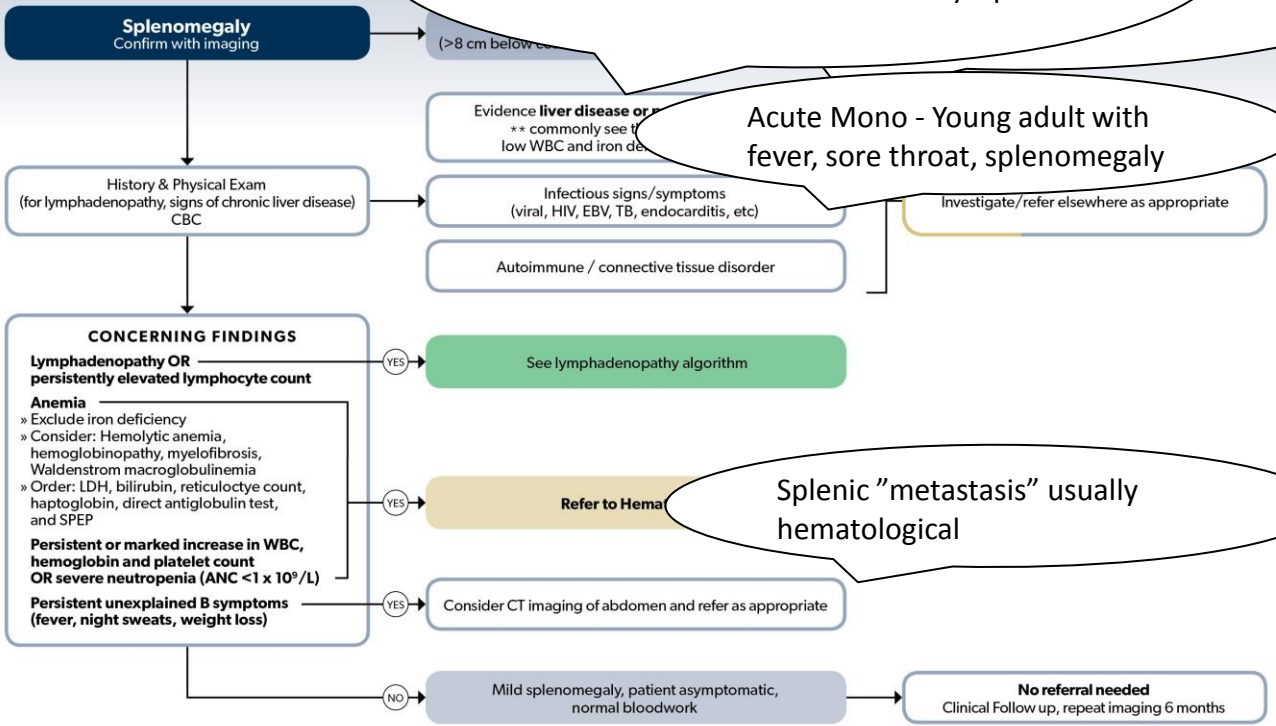
Splen

In registry study ½ with hepatic splenomegaly had hepatomegaly, signs of chronic liver disease or thrombocytopenia

Acute Mono - Young adult with fever, sore throat, splenomegaly



Splenic "metastasis" usually hematological

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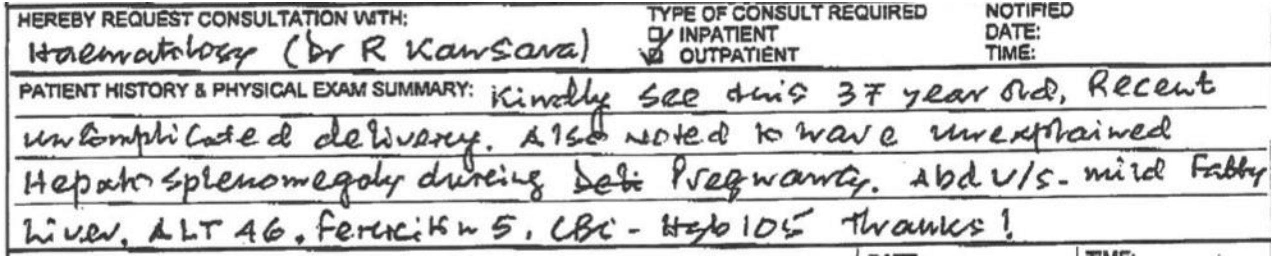
Splenomegaly Referral 2


HEREBY REQUEST CONSULTATION WITH: Haematology (Dr R Kansara)

TYPE OF CONSULT REQUIRED ☐ INPATIENT ☑ OUTPATIENT

NOTIFIED DATE: TIME:

PATIENT HISTORY & PHYSICAL EXAM SUMMARY: Kindly see this 37 year old, Recent uncomplicated delivery. Also noted to have unexplained Hepatosplenomegaly during pregnancy. Abd U/S - mild fatty liver, ALT 46, ferritin 5, CBC - Hgb 105 thanks!

US- fatty liver spleen 15 x 11 x 5 cm

Followed up in 3, 9 months, slight improvement post partum, no other change

CT mild splenomegaly, fatty liver

Nothing on exam or history that was concerning only iron deficiency anemia. Significant patient anxiety, marrow done – normal.

Practice Points

- Radiology does not always give measurement or degree of variation from upper limit normal
- If non palpable spleen and patient is well without abnormalities on CBC
  - No need for referral, follow clinically & with imaging repeat in 6 months

Learning Objectives

1. To be able to determine if splenomegaly is concerning
2. In a patient with splenomegaly know clinical context where Hematology referral is beneficial
3. When a patient has lymphadenopathy appreciate an approach to investigation and when to suspect lymphoma

Suspicion of lymphoma

- Most patients initially present to primary care provider
- >30% patients with NHL and > 40% HL have more than 3 visits to Primary Care before investigations/ referrals
- No symptom signature

1. Lyratzopoulos G, Neal RD, Barbiere JM, et al. Variation in number of general practitioner consultations before hospital referral for cancer: findings from the 2010 National Cancer Patient Experience Survey in England. Lancet Oncol 2012; **13(4):** 353–365.Cancer, N. C. C. f. (2014)

Suspicion of Lymphoma

- lifetime probability NHL 2 %
- very few factors greatly increase risk
  - Primary Immune Disorders (incidence lymphoma 12-25%)
  - Autoimmune Disease, Organ Transplant, HIV, Drugs that modulate immune system

Suspicion of Lymphoma

- IF first degree relative with NHL, HL or CLL

  ~1.7 fold, 3.1 fold and 8.5 fold risk respectively of same diagnosis

- Thus lifetime risk NHL ~ 3.4% *even lower specific lymphoma subtypes*

Suspicion of lymphoma

- Most cases NHL and HL present with lymphadenopathy (LN)
  - Positive Predictive Value [PPV] 18.6% (patients > 40)
- B symptoms - aggressive lymphomas with high disease burden
  - In isolation neither PPV or Negative Predictive Value (NPV) that high

1. Shephard, E.A., et al., *Quantifying the risk of non-Hodgkin lymphoma in symptomatic primary care patients aged >/=40 years: a large case-control study using electronic records.* Br J Gen Pract, 2015. **65**(634): p. e281-8.
2. Shephard, E.A., et al., *Quantifying the risk of Hodgkin lymphoma in symptomatic primary care patients aged >/=40 years: a case-control study using electronic records.* Br J Gen Pract, 2015. **65**(634): p. e289-94.

Suspicion of lymphoma

- Other clinical signs/ symptoms in isolation low predictive value
- Increased PPV of LN for lymphoma
  - Weight loss, abdominal complaints, dyspnea
  - Leukocytosis, cytopenia, increased liver enzymes, increased inflammatory markers

1. Shephard, E.A., et al., *Quantifying the risk of non-Hodgkin lymphoma in symptomatic primary care patients aged >/=40 years: a large case-control study using electronic records.* Br J Gen Pract, 2015. **65**(634): p. e281-8.
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Work-Up of Lymphadenopathy Suspicious for LYMPHOMA

Timeline and Legend pg.5

RISK FACTORS: HIGH risk: immune deficiency (ie. HIV or organ transplant), autoimmune disease +/- immune suppressing medications, and history of lymphoma

PRACTICE POINTS: ***Consider your differential diagnosis*** -reactive LN due to infection (ie:TB) or inflammation, metastatic malignancy and autoimmune disease. This document applies to adults 17 years of age or older.

PRACTICE POINTS: **All referrals sent within 24 hrs of visit.** Provide complete information as requested to avoid delays. Ensure patient and family is well informed and receives appointment information. If patient is in distress, offer referral to local counsellor. See ***Supporting Information for Clinicians*** (pg 4) for contacts and resources. Contact the **Cancer Question Helpline for Primary Care** for assistance.

Emergent
- Airway compromise
- Superior vena cava compression
- Spinal cord compression

→ **Send to Emergency Department**

Palpable Lymphadenopathy (LN)
- Abnormal LN: >2-3 cm, persistent enlargement & without obvious cause

Lymphadenopathy on Imaging

→ **History & Physical Exam**
*** Consider your differential diagnosis****
Order CBC, HIV test, Chest X-ray

→ **No ↑ Lymphocyte Count**

High Suspicion / Concerning Features
PROCEED without delay
- HIGH Risk Patients (as above)
- LN + Abnormal Bloodwork (severe anemia, thrombocytopenia, pancytopenia)
- Widespread LN +/- splenomegaly or bulky LN (mass >6cm)
- Mediastinal mass
- LN with rapid growth
- LN & B symptoms (drenching sweats, unexplained fever, weight loss)
- Patient symptomatic from abnormal LN (ie: short of breath, abdominal pain)

If ANY Concerning features - Determine* best site for diagnostic biopsy
- **Order URGENT CT scans if not already done,** including neck, chest, abdomen & pelvis
- **Preference for site of biopsy:** Palpable >Mediastinal >CT guided
- **Order CBC, chemistry (including Ca, LDH, Cr) and INR if not already done**

**if assistance is needed contact Hematologist on call for advice*

→ **Continue to Diagnostic pathway pg.2**

If NONE Clinical Follow up → **Persistent / progressive LN** on exam (>4weeks) or imaging (after serial examination)

↑ Lymphocyte Count → **Order flow cytometry on peripheral blood** (query CLL vs other lymphoma) → **Positive for CLL or monoclonal lymphocyte population** → **REFER TO CCMB**

In Sixty → In Sixty timeline starts with evidence of concerning features

In Sixty → All imaging done within 2 weeks

Initial Steps

- History, examine all LN groups
  - Size, consistency, rapidity of growth
  - Local cause
  - Oropharynx, liver, spleen
- CBC, Chest x ray, HIV test
- CT scan is imaging test of choice in adults

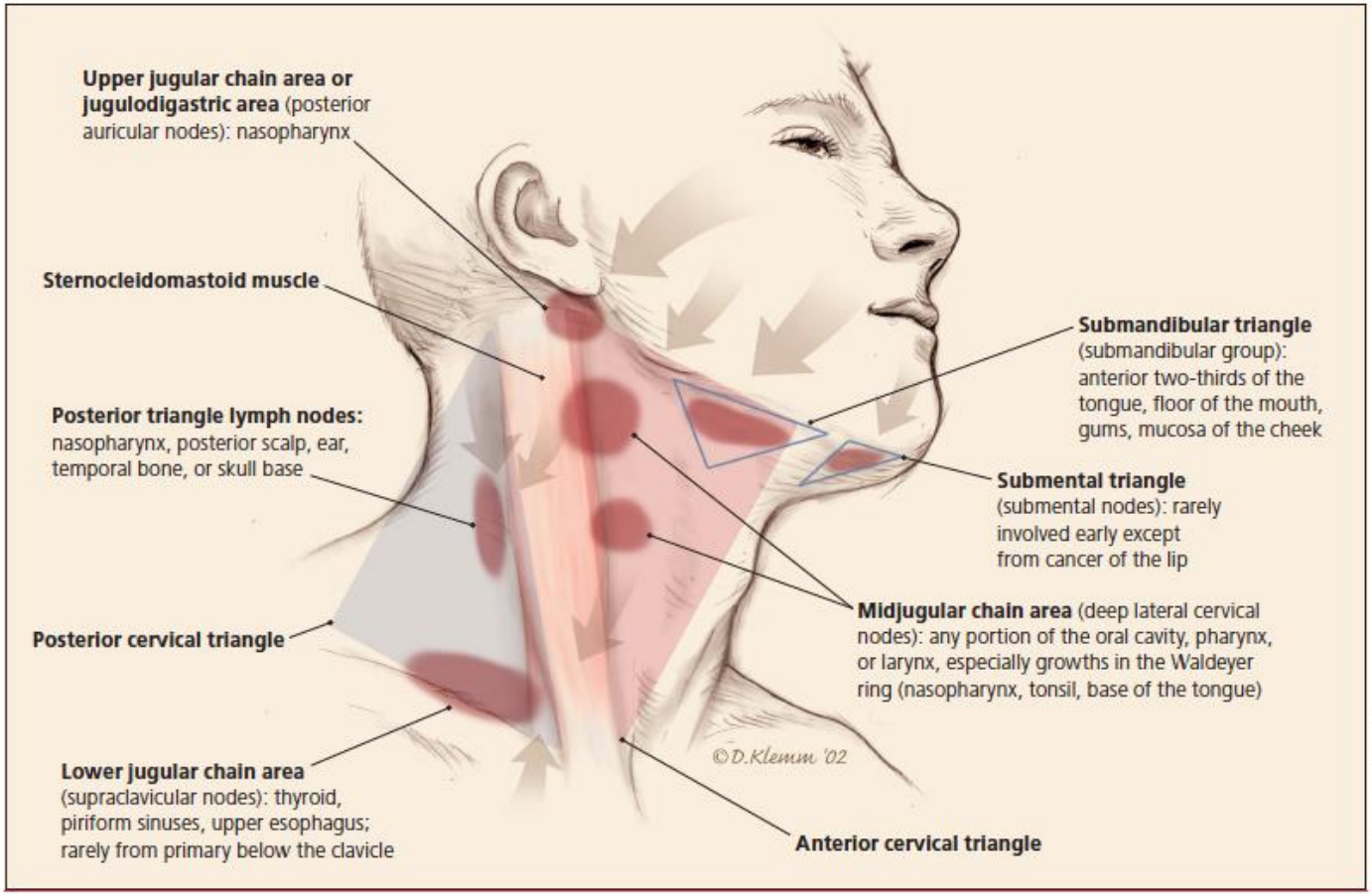

Figure 1. Cervical triangle anatomy with common lymph node locations and drainage areas.

Lateral Neck Mass

- Most commonly benign- infection/ inflammation
  - odotogenic, salivary, viral or bacterial etiologies
  - Recent Ear, Nose, Throat symptoms good NPV
- More concerning for malignancy
  - Lymphoma up to 50% malignant lateral neck mass[1]
    - Older patients (>40), persistent, rapidly growing, weight loss, sweats

1. Yeo J, et al. Clinical otolaryngology, 2013.
2. Herd MK, et al. Br J Oral Maxillofac surgery 2012;50:309-13.

Lymphadenopathy (LN) + HIGH Risk patient

LN + anemia, thrombocytopenia or pancytopenia

Widespread LN +/- splenomegaly or bulky LN (mass >6cm)

Mediastinal mass

LN with rapid growth or B symptoms (drenching sweats, unexplained fever, weight loss)

Patient symptomatic from abnormal LN (ie: short of breath, abdominal pain)

IN SIXTY CANCER ACTION

Work-Up of Lymphadenopathy Suspicious for LYMPHOMA

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In Sixty → In Sixty timeline starts with evidence of concerning features

In Sixty → All imaging done within 2 weeks

IN60_LYMS: 03-06-2015

Referral

Dear Doctor,

I would appreciate you assessing this 23 year old male who presented to ER on March 9th with a history of shortness of breath for a few months, generalized puritis and fevers on and off. He had decreased air entry in his left lung and was found subsequently on CT to have a large mass in his left lung with mediastinal nodes and later on CT abdomen & pelvis to have an enlarged spleen. Dr

Examine patient, get CBC, biochem (including Ca, LDH), HIV, INR

Axillary LN found

Diagnostic Pathway LYMPHOMA

Timeline and Legend pg.5

PRACTICE POINTS: Consultation with the Lymphoma Disease Site Group can happen earlier in the pathway if clinicians need additional support or guidance.

*Results Consistent with Lymphoma: ***If flow cytometry from biopsy or FNA is consistent with lymphoma, consult should be sent to CCMB Central Referral for triage by Lymphoma DSG even if final pathology report is not yet complete.***

PRACTICE POINTS: Ensure patient is well informed and receives appointment information. Offer patients connections with psychosocial clinicians and cancer navigation services (see ***Supporting Information for Clinicians***, pg 4). Ensure the referring primary care provider is informed of results, direct referrals, and result discussions with patients.

Diagnostic Biopsy
IF THERE IS A PALPABLE MASS, DO NOT WAIT FOR CT RESULTS TO SEND CONSULT TO SURGEON:

- **Order URGENT CT scans if not already done,** including neck, chest, abdomen & pelvis
- **Preference for site of biopsy:** Palpable >Mediastinal >CT guided
- For CT-guided biopsy of Intra-abdominal LN review CT Neck, Chest for alternate LN first
- **Order CBC, chemistry (including Ca, LDH, Cr) and INR if not already done**

Neck LN:
-Surgery Consult for Biopsy with FNA

Alternate Diagnosis → Refer to appropriate provider

FNA consistent* with Lymphoma SURGEON books Open Biopsy AND Direct Refers to CCMB Lymphoma → **Biopsy** (1-2 wks) sent Lymphoma protocol

Axillary or Inguinal LN:
Surgeon assessment → **Open biopsy** (same day or book O.R. within 2 weeks) sent Lymphoma protocol

Mediastinal Mass:
Surgeon Assessment → **Biopsy by mediastinoscopy** (±PAC) (O.R. within 2 wks) sent

12% patients

Intra-abdominal/ retroperitoneal LN:
Provider orders CT guided biopsy (no surgical referral needed) → **FNA and core biopsies** recommend 18guage or larger; sent Lymphoma protocol

Results consistent* with Lymphoma
Provider Direct Refers to CCMB Lymphoma

Clinical suspicion remains despite negative results → **Refer to Lymphoma DSG for review**

Negative for cancer & lymphadenopathy resolved → Send back to Primary Care Provider to inform patient of results.

Triaged by Lymphoma DSG
-if Concerning features proceed with booking first appointment with hematologist when pathology anticipated to be available.
(~14 days after biopsy)

Continue to Triage & Treatment pathway pg.3

In Sixty: FNA results reported within 2 days (immediate direct referral to CCMB if suspicious of lymphoma)

In Sixty: Biopsy with 2 weeks of surgery consult/assessment/FNA

In Sixty: Biopsy results reported within 14 days. Immediate direct referral to CCMB if suspicious of lymphoma)

FOR REVIEW: IN60_LYMS: 29-06-2015

Diagnosis of lymphoma

- FNA – exclusion metastatic carcinoma, cannot be used for definitive diagnosis
- Open (preferred) or core biopsy required for lymphoma
  - Biopsy should be sent “LYMPHOMA PROTOCOL” if lymphoma in differential diagnosis

Practice Challenges

- Many patients with benign lymphadenopathy
- Knowing where to send patient for LN biopsy, how/ when to arrange CT guided biopsy
- What to do with rapidly deteriorating patient with concerning features

Take home message(s)

- Important to rule out hepatic splenomegaly
- Infectious causes splenomegaly common especially in young patient
  - Often have fever
- algorithm helps to identify patients who most benefit from Hematology referral
  - Patients with “scanomegaly” only can be observed

Take home message(s)

- Always include physical exam (ie palpable nodes – size/ location) and whether there are concerning symptoms with consult
- In Sixty Clinical Pathway for lymphadenopathy highlights when to be most suspicious of lymphoma and approach

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Thank you

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