Pediatric Telehealth Rounds

Today's topic:

Red Flags for Pediatric Cancer

Speaker:

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PGY 3 Pediatrics Resident

April 8, 2016

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Declaration of conflict

Speaker has nothing to disclose with regard to commercial support.

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CASE

- 4 year old female, previously healthy
- Decreased appetite, subjective weight loss, fatigue, pallor x 2 weeks
  - No shortness of breath
  - No night sweats
  - No bony pain
- Seen at rural nursing station 2 days ago after 2 episodes of epistaxis, resolved spontaneously after 1 hour
  - No bruising, petechiae
- Returned to nursing station for fever, sore throat
  - No other viral URTI symptoms

CASE

- O/E: febrile, **pale++, tachycardic**, other VSS
  - Normal respiratory and CVS exams
  - No palpable masses, HSM
  - No petechiae or bruising
  - No significant LAD
  - MSK exam unremarkable
- CBC done due to significant pallor → anemia, thrombocytopenia
  - WBC normal
  - Smear – no blasts
- Admitted to rural hospital for W/U of bicytopenia
  - Repeat CBC in few days: **pancytopenia with peripheral blasts** → transferred to CHEO
  - CXR – no mediastinal mass
  - Tumor lysis bloodwork (Mg, PO4, iCa, uric acid) unremarkable

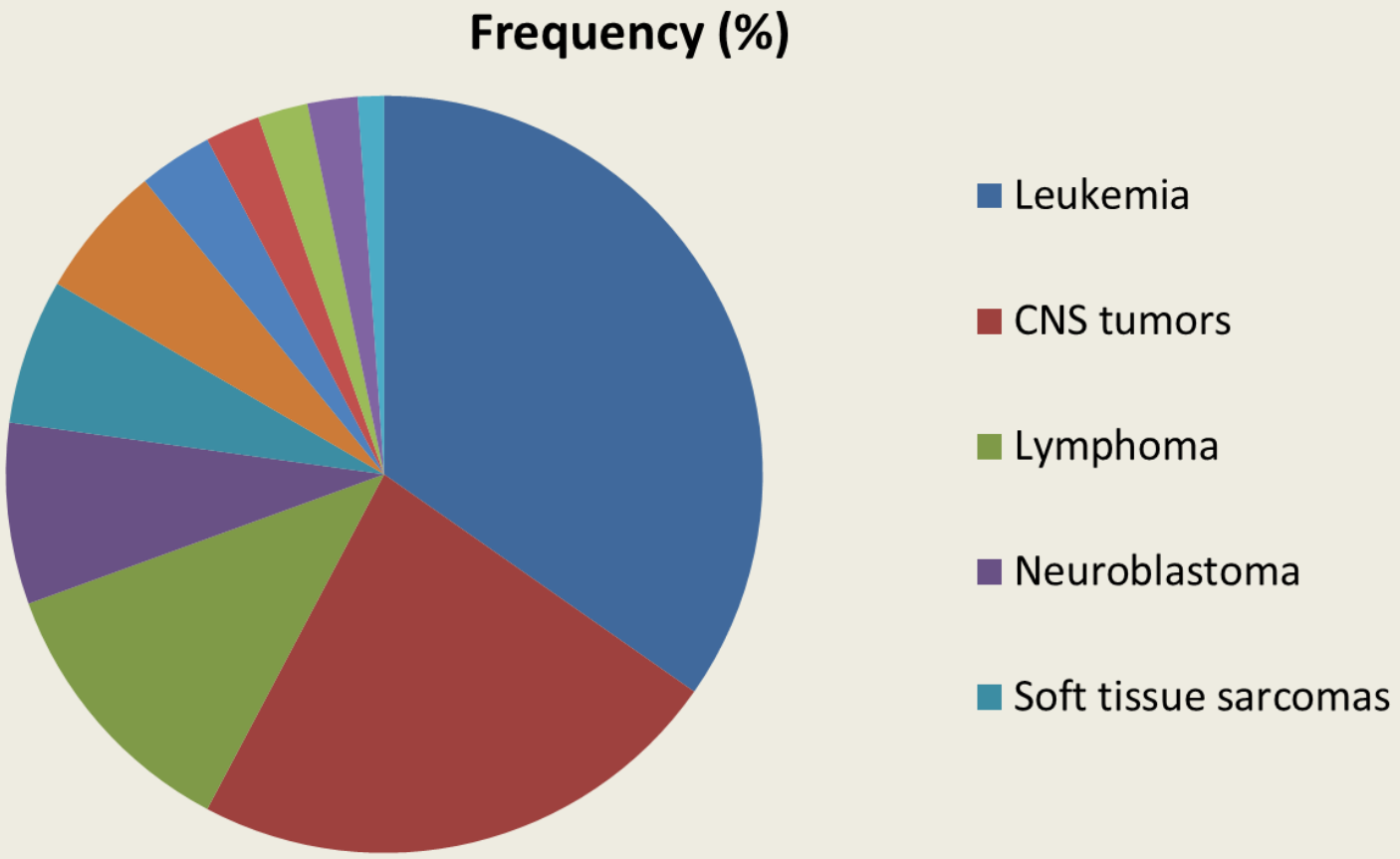
LEARNING OBJECTIVES

- Epidemiology of childhood cancers
- Factors influencing delays in diagnosis
- Medical conditions and syndromes associated with increased risk for pediatric cancers
- Approach to assessment and initial evaluation of red flags:
  - Constitutional symptoms/fever
  - Lymphadenopathy
  - Headache/CNS symptoms
  - Bone and joint pain
  - Abdominal mass
  - Mediastinal mass/respiratory distress
  - Abnormal CBC
- Quick overview of initial management of oncologic emergencies

INTRODUCTION

- Pediatric cancers are rare events overall – 15 in 100 000[1]
  - Most common cause of disease-related mortality in children
- 5 year survival rates differ based on type of malignancy → 84% in Canada[2]
- Early treatment associated with improved prognosis, fewer complications from disease and therapy
  - **Early recognition of red flags and referral to Pediatric Oncology essential**

EPIDEMIOLOGY OF CHILDHOOD CANCERS[3]



COMMON MALIGNANCIES BY AGE GROUP[4]

< 1 year	1-4 years	5-9 years	10-14 years	15-19 years
• Neuroblastoma • Leukemias • Germ cell tumors	• Leukemias • CNS tumors • Neuroblastoma • Wilm's	• Leukemias • CNS tumors • Neuroblastoma	• Leukemias • CNS tumors • Lymphoma • Soft tissue sarcomas	• Leukemias • Lymphoma • CNS tumors • Soft tissue sarcomas

DIAGNOSTIC DELAYS IN PEDIATRIC CANCERS[1,5]

- Age of patient
  - Trend towards longer diagnostic delay for older children
- Type of malignancy
  - CNS tumors, bone tumors associated with greater diagnostic delay than leukemias or Wilm's tumors
- Socioeconomic factors
  - Distance from urban centre
  - Type of provider seen at presentation

RISK FACTORS[1]

Syndrome/Disorder	Associated Malignancies
Down syndrome	ALL, AML
Neurocutaneous syndromes (NF, TSC, von Hippel-Lindau disease)	Optic glioma, CNS tumor, neurofibrosarcoma, peripheral nerve sheath tumor, leukemia, Wilm's tumor
Turner syndrome	Gonadoblastoma
Hemihypertrophy syndromes (Beckwith-Wiedemann)	Hepatoblasoma, Wilm's tumor
Denys-Drash syndrome	Wilm's tumor
WAGR syndrome	Wilm's tumor
Immunodeficiency disorders (Wiskott-Aldrich, common/severe combined immunodeficiency)	Leukemia, non-Hodgkin lymphoma

COMMON RED FLAGS FOR PEDIATRIC MALIGNANCY[1,4]

- Unexplained fever, weight loss
- Lymphadenopathy
- Headache, neurologic deficits
  - Loss of milestones, macrocephaly in infants
- Bone and joint pain
- Palpable abdominal mass
- Mediastinal mass
  - Associated cardiorespiratory symptoms
- Excessive bruising, bleeding, pallor
  - Blood count abnormalities

CONSTITUTIONAL SYMPTOMS[1,4]

Prolonged Fever/Fever of Unknown Origin

- 2-9% of FUO cases associated with malignancy
- Can be the only presenting complaint in leukemia, lymphoma
  - Tumor-related necrosis in neuroblastoma, Wilm's
- "B symptoms" seen in Hodgkin lymphoma

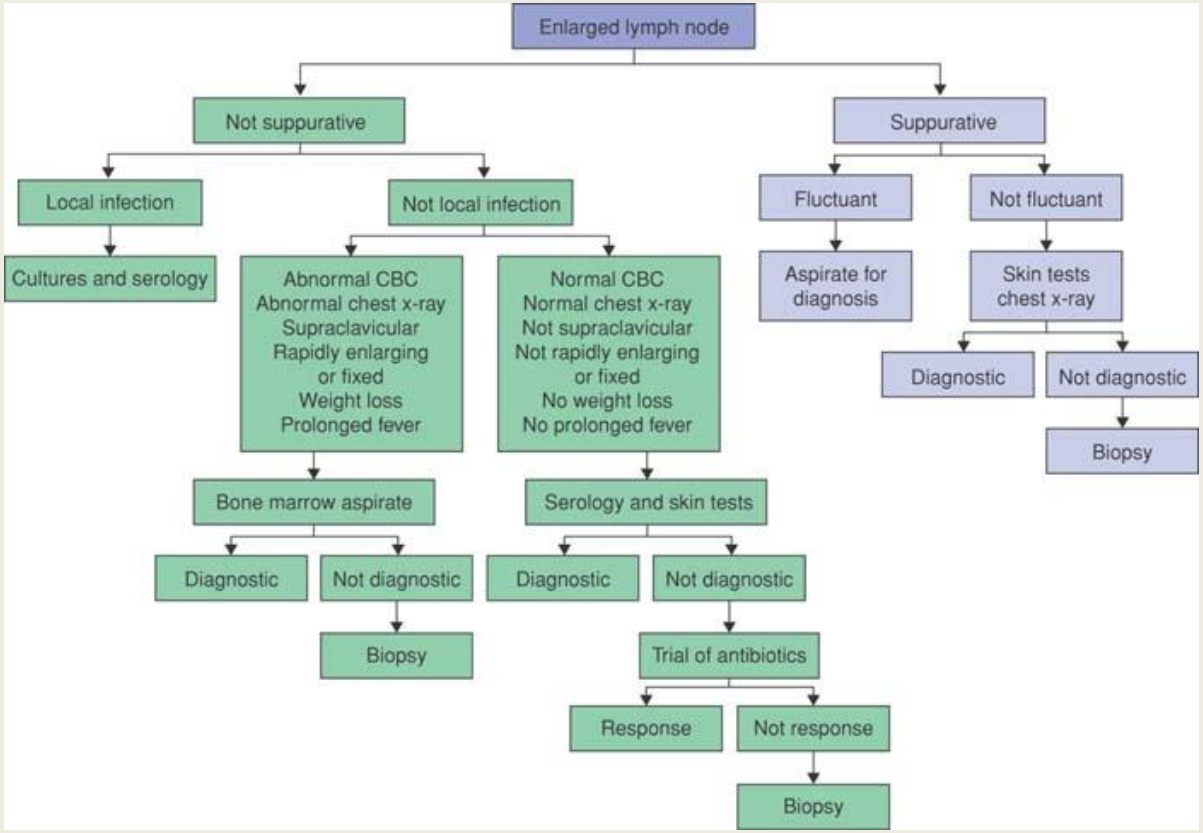
Evaluation

- History and physical exam:
  - Pallor/bleeding/petechiae?
  - Weight loss?
  - Bony pain?
  - Lymphadenopathy?
  - Abdo mass, HSM?
- Labs:
  - CBC+D, smear
  - LDH
  - Lytes, Mg, PO4, iCa uric acid
- Imaging
  - CXR → ?mediastinal mass
  - Abdo US → ?masses, HSM

LYMPHADENOPATHY[1]

- LNs enlarged if > 10 mm
  - >5mm for epitrochlear; >15mm for inguinal
- Most common etiology reactive/infectious
- More likely to be malignant if:
  - Constitutional symptoms present
  - Firm, rubbery, matted, non-tender, progressive in size
  - Location: posterior auricular, epitrochlear, supraclavicular
- Cancers associated with H&N LAD
  - Neuroblastoma, rhabdomyosarcoma, NHL, leukemia (< 6 yrs)
  - HL, NHL (7-13 yrs)
  - HL (> 13 yrs)

Lymphadenopathy – Evaluation[1]



HEADACHE[1,4]

Signs and symptoms of CNS tumors vary with age:

- Infants more likely to present with macrocephaly, lethargy, irritability, developmental delay

Most common symptoms overall at presentation:

- Headache
- N/V
- Abnormal gait and coordination

Evaluation

(1)Detailed history

- Location – occipital most concerning
- Early morning or waking child from sleep
- Personal/FHx migraines, migraine features
- ROS – association with neurologic deficits

(2) Full neurologic exam including fundoscopy

(3) Consider neuroimaging – MRI preferred

Headache – Red Flags for Neuroimaging[4]

- Persistent headache + any of:
  - Wakes child from sleep
  - Occurs upon waking
  - Child < 4 years
  - Associated with disorientation or confusion
- Persistent vomiting upon waking
- Visual findings
  - Papilledema, optic atrophy, new nystagmus, reduced acuity not due to refractive error, visual field defects, proptosis
- Motor findings
  - Motor regression, focal weakness, abnormal gait/coordination, Bell's palsy not improving over 4 weeks, swallowing difficulty
- New onset afebrile seizures or decreased LOC

BONE AND JOINT PAIN[1,4]

- Malignancies involving bone or bone marrow present with pain
- Ewing sarcoma, osteosarcoma: 80-90%
  - Localized pain at site of involvement
  - +/- associated soft tissue mass
- Acute leukemia: 21-33%
  - Multifocal bone pain
  - ALL > AML present with bone pain

Bone and Joint Pain – Evaluation[1,4]

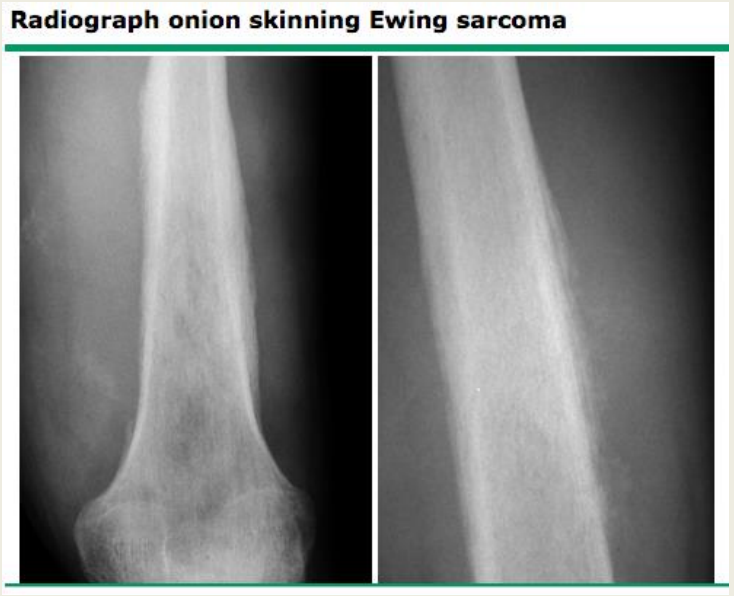
Challenging to differentiate neoplastic vs. rheumatologic/infectious etiology

(1) History and Exam

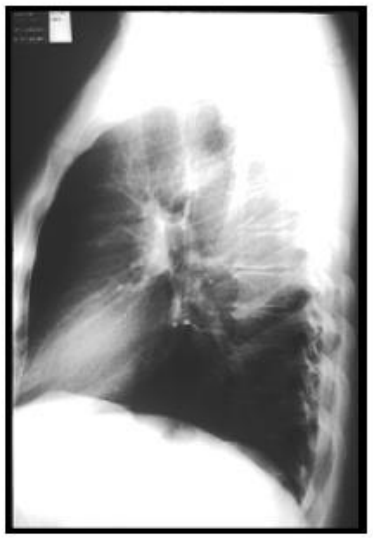
- Pain disproportionate to signs of inflammation
- Worse at night, no AM stiffness
- Shifts in location, bone and joint pain (for leukemia)
- Constitutional symptoms

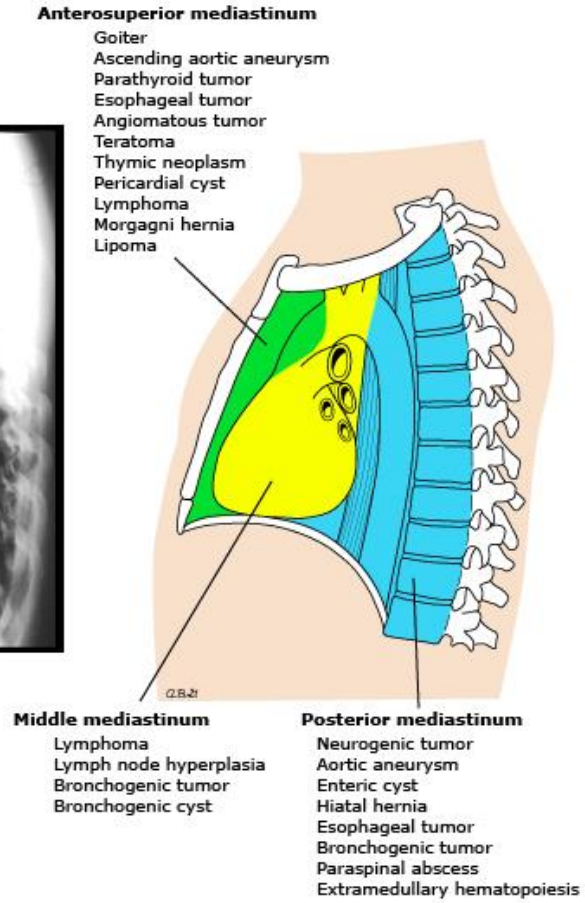
(2) Initial Investigations

- CBC – cytopenias, blasts
- LDH
- Lytes, Mg, PO4, iCa, uric acid – tumor lysis
- XR – "onion skin" or "sunburst" appearance in sarcomas
  - Lytic/sclerotic lesions, periosteal rxn in leukemia



MEDIASTINAL MASS AND RESPIRATORY DISTRESS[4]





Anterior – "4T's"

- Terrible tumors: HL/NHL, T-cell ALL, rhabdomyosarcoma, Ewing's
- Thymoma
- Teratoma
- Thyroid

Middle – lymphoma, extension from intra-abdominal tumors

Posterior – neurogenic tumors (neuroblastoma); less commonly Ewing, lymphoma, rhabdomyosarcoma

Mediastinal Mass – Evaluation[1,4]

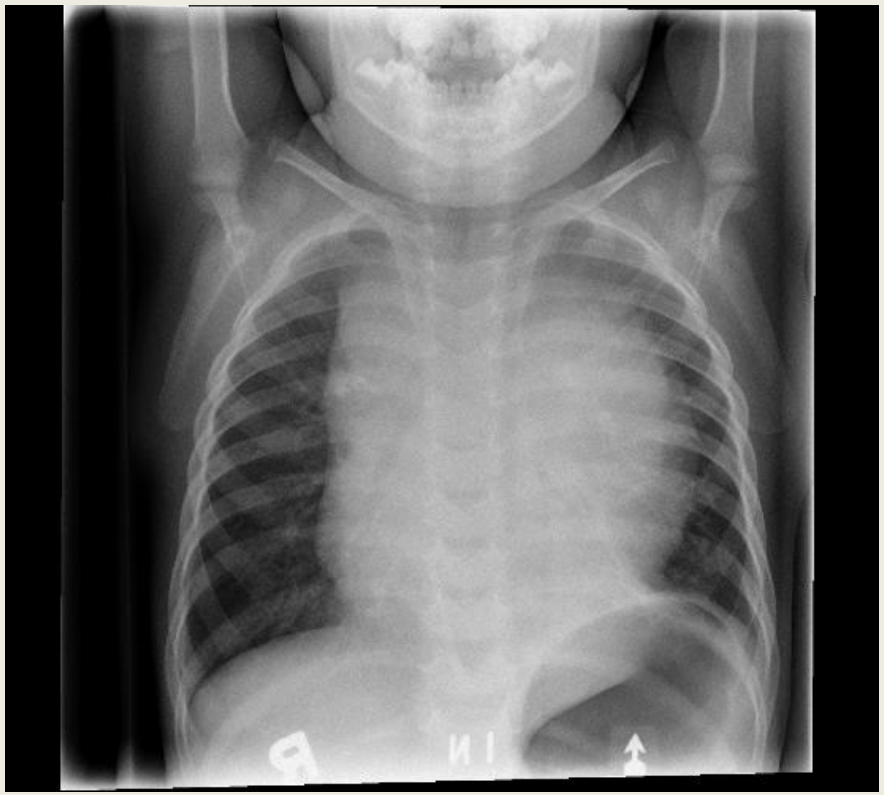
History and Exam

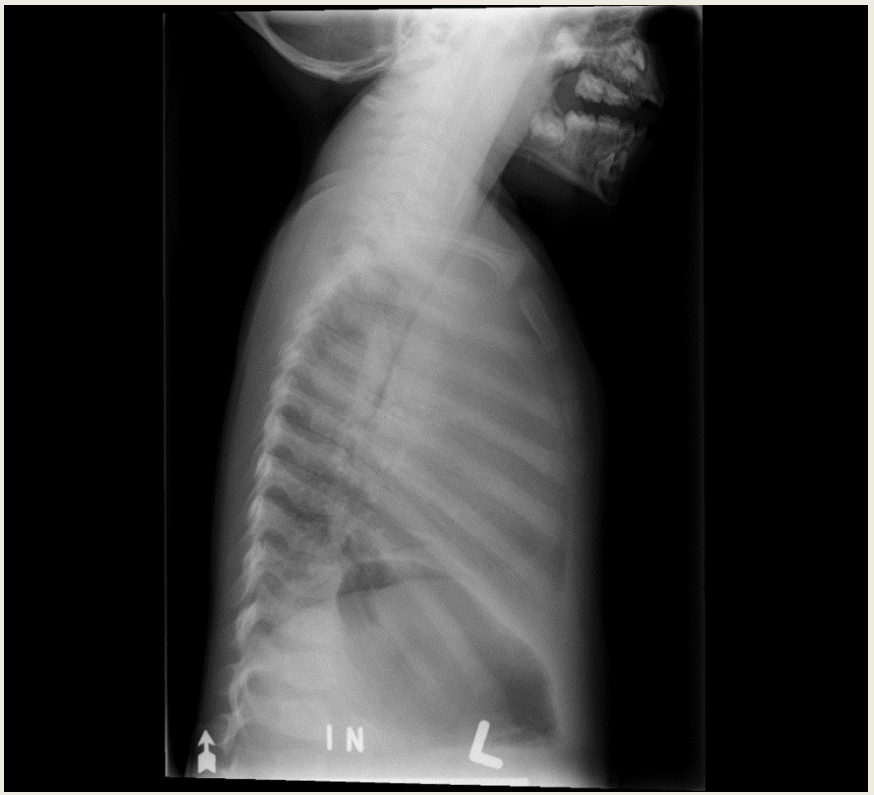
- Airway compression – stridor, wheeze, SOB, hoarse voice, cough
- SVC syndrome – facial swelling/plethora, increased ICP
- Esophageal compression – dysphagia
- Restriction from pericardial effusion/tamponade or mass obstructing outflow – signs of reduced cardiac output

Initial Investigations

- CBC – cytopenias, blasts
- Tumor lysis bloodwork – lytes, Mg, PO4, iCa, uric acid, LDH
- CXR → if confirmed, will need CT chest +/- bone marrow aspirate & biopsy

Mediastinal Mass – Evaluation[6]





PALPABLE ABDOMINAL MASS[1,4]

- Most common intra-abdominal tumor – Wilm's, neuroblastoma
  - Others: abdominal lymphoma, hepatic or ovarian tumor, soft tissue sarcoma
- Age helps narrow ddx
  - Congenital GI/GU malformations - neonates
  - Wilm's tumor, neuroblastoma – infants and young children
  - Leukemic/lymphomic infiltration of liver, spleen, retroperitoneal LNs – older children
    - Abdominal lymphoma commonly Burkitt's

Abdominal Mass – Evaluation[1,4]

History and Physical Exam:

- GU symptoms – hematuria, decreased UO
- Constitutional symptoms
- FHx of hepatoblastoma, HCC
- Location of abdominal mass
- Aniridia, hemihypertrophy, GU malformations
  - Wilm's tumor (WAGR)
- Subcutaneous nodules, periorbital ecchymosis, opsoclonus-myoclonus
  - Neuroblastoma
- Signs of precocious puberty → liver/gonadal/germ cell tumors

Location	Malignant Mass	Benign Mass
Upper abdomen	Wilm's tumor Neuroblastoma Leukemia/lymphoma Hepatoblastoma/HCC Germ cell tumors Sarcomas	Hydronephrosis Multicystic/polycystic kidney Pyloric stenosis Splenomegaly Choledochal cyst Intestinal duplication
Mid abdomen	NHL Neuroblastoma Germ cell tumors Sarcomas	Intestinal duplication Mesenteric cyst
Lower abdomen and pelvis	Ovarian tumors Germ cell tumors Sarcomas	Ovarian cyst Hydrometrocolpos Bladder obstruction

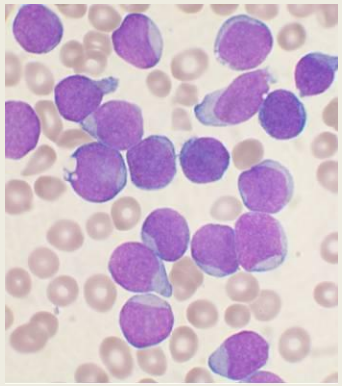
Abdominal Mass – Investigations[1,4,5]

Initial Investigations

- CBC
- AST, ALT
- BUN, Cr, urinalysis
- Lytes, Mg, PO4, iCa, uric acid (for tumor lysis)
- LDH
- Consider tumor markers
  - Urinary catecholamines (neuroblastoma)
  - AFP (hepatoblastoma, germ cell tumors)
  - Beta-hCG (hepatoblastoma, germ cell tumors)
- Abdominal US
- CXR

Blood Count Abnormalities – Cytopenias[1,4]

- Acute leukemias → infiltrate and suppress BM
  - Up to 90% at dx have anemia or thrombocytopenia or both
- Neuroblastoma, lymphoma, Ewing sarcoma, rhabdomyosarcoma can also infiltrate BM



Acute lymphoblastic leukemia – peripheral smear

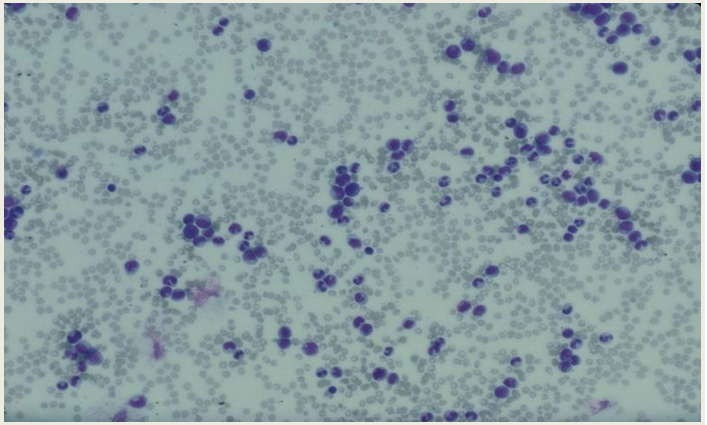
Evaluation

History and Physical Exam:

- Pallor, respiratory distress, fatigue, palpitations
- Fever, frequent infections
- Easy bruising or mucosal bleeding, petechiae
- Constitutional symptoms, bony pain
- Examine for LAD, HSM

Blood Count Abnormalities – Leukocytosis, Thrombocytosis[1]

- ~50% of children with new dx acute leukemia have WBC > 20
- WBC >100 pathognomonic of malignancy
  - Common in pre-B and T cell ALL, AML – usually blasts present
- Eosinophilia
  - Pre-B ALL → paraneoplastic process
  - Hodgkin lymphoma
  - Other ddx: parasitic infections, hypersensitivity reactions
- Thrombocytosis
  - Most common in CML, hepatoblastoma, neuroblastoma



Peripheral smear - hyperleukocytosis

Blood Count Abnormalities – Initial Investigations[1,4]

- CBC + differential, peripheral smear, reticulocytes
  - If blasts seen on peripheral smear → leukemia until proven otherwise!
- LDH
- Uric acid, PO4, iCa, Mg, lytes (tumor lysis)
- CXR – r/o mediastinal mass
- AUS if clinically indicated – r/o mass, HSM

Indications for referral and consideration of BMA/biopsy

- 1+ cell lines depressed
- Blasts or leukoerythroblastic changes on peripheral smear
- Unexplained LAD or HSM
- Mediastinal mass or abdominal mass
- Absence of infectious cause for blood abnormality

OTHER RED FLAGS BY SYSTEM[1,5]

Signs and Symptoms	Initial Work-Up	Major Associated Tumors
Endocrine: Growth failure, DI/SAIDH, precocious puberty, galactorrhea	<u>HP Axis function:</u> TSH, fT4 Prolactin AM cortisol Serum Na, osmolality GH, IGF-1 AFP, beta hCG (for germ cell tumors)	Hypothalamic tumors Pituitary tumors Gonadal/adrenal tumors
Ophthalmologic: Leukocoria, proptosis, reduced acuity, strabismus	Ophthalmology evaluation Urine catcholamines (for neuroblastoma)	Retinoblastoma Metastatic rhabdomyosarcoma Neuroblastoma
Genitourinary: Testes, vaginal mass	CBC+diff AFP, beta hCG UA Abdo/pelvis US	Germ cell tumor Rhabdomyosarcoma Adrenal tumor
CVS: Hypertension	Urine catecholamines (neuroblastoma) UA, lytes, BUN/Cr (renal tumor) CXR Abdominal US	Neuroblastoma Renal tumor Adrenal tumor

Initial Management of OncoloGic Emergencies – Clinical Pearls

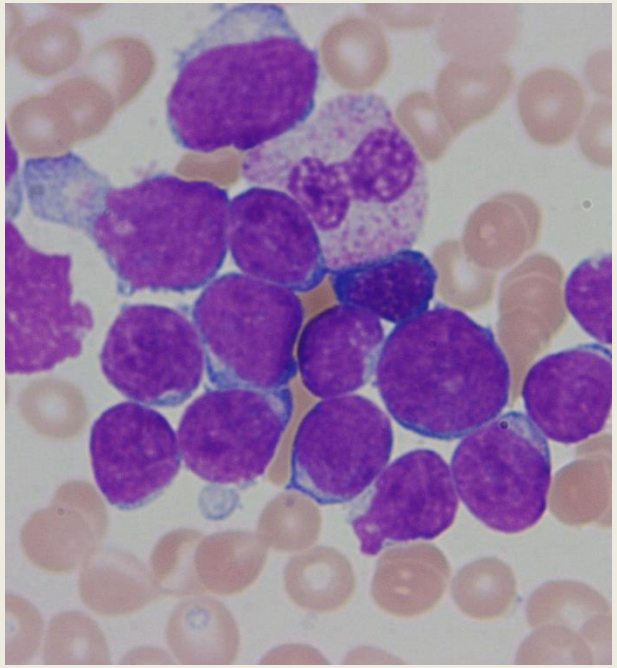
In your investigations for a child with suspected cancer, you may encounter the following oncologic emergencies:

- Tumor lysis syndrome
- Superior mediastinal syndrome/SVC syndrome
- Spinal cord compression
- Febrile neutropenia

Involve Pediatric Oncology from your nearest tertiary care centre early!

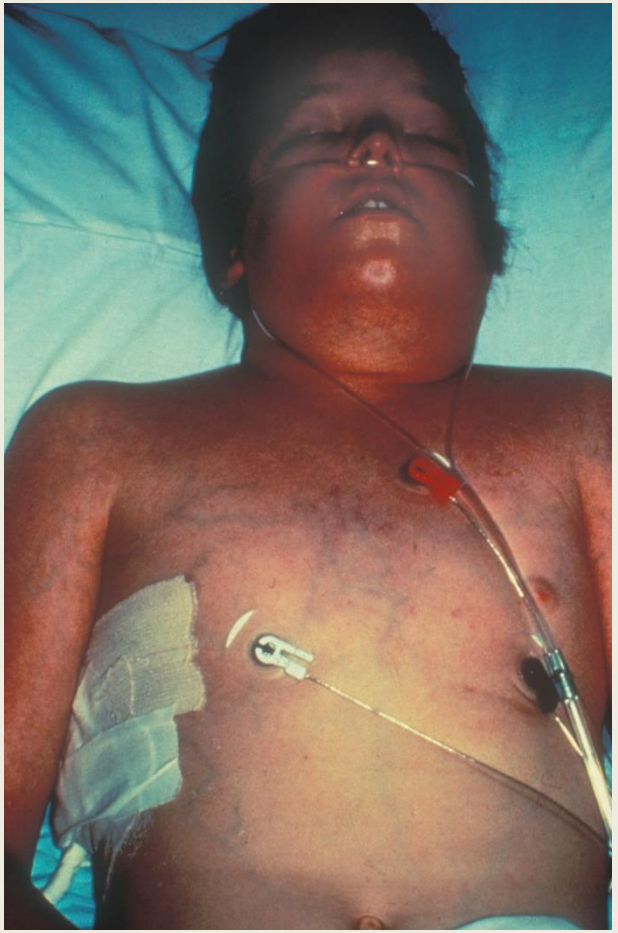
TUMOR LYSIS SYNDROME[6]

- Hyperuricemia
  - Allopurinol or rasburicase
  - Hydration
- Hypocalcemia
  - Do NOT treat with IV calcium (risk of arrhythmia) unless EKG changes and symptomatic
- Hyperkalemia
  - Kayexalate, insulin with glucose, or ventolin



SUPERIOR MEDIASTINAL/SVC SYNDROME[6]

- SVC compression → reduced venous return to heart, increased venous pressure to H&N
- No anesthesia! No sedative meds!
- ABC's:
  - **A** – keep patient upright, have BVM +/- intubation equipment ready
  - **B** – O2, monitor resp distress
  - **C** – assess for signs of reduced CO
  - *Metabolic – high risk for tumor lysis (especially if Burkitt's lymphoma)



SUPERIOR MEDIASTINAL/SVC SYNDROME[6]

Draft #4

GUIDELINES FOR THE MANAGEMENT OF PATIENTS WITH A MEDIASTINAL MASS OR A LARGE ABDOMINAL MASS

Purpose	To provide co-ordinated/multidepartmental approach to the child/adolescent presenting with a mediastinal or large abdominal mass

Any patient with a newly identified mediastinal or large abdominal mass who is not already admitted to hospital and requires urgent assessment or intervention should be immediately referred to the Emergency department.

In the Emergency room:

- Document:
  - vital signs and O_2 sat on room air
  - if patient can lie flat
  - If evidence of SVC syndrome (upper body plethora, swelling of upper limbs, cough or voice change)
- Start tumour lysis protocol

If in danger of respiratory arrest:

- keep patient calm
- position patient to optimize their breathing eg. prone
- make NPO
- notify Anesthesia, Surgery, Oncology, ICU and ENT if indicated

SPINAL CORD COMPRESSION[6]

- 4% of children with cancer develop acute cord or cauda equina compression
- Half of cases caused by sarcomas
  - Others – neuroblastoma, lymphoma, leukemia, CNS tumors
- Symptoms:
  - Back pain with localized tenderness (most common)
  - Incontinence, urinary retention, bowel function abnormalities
  - Decreased LL strength, sensory deficits
- Child with known history of cancer and back pain should be presumed to have cord involvement until proven otherwise!
- Involve Oncology and Neurosurgery early
  - Emergent MRI
  - Dexamethasone

FEBRILE NEUTROPENIA

- Risk of bacterial and fungal infection when ANC < 0.5
- Send blood cultures (central and peripheral); other cultures as clinically indicated (urine, NP aspirate, etc.)
- First line antibiotics at CHEO:
  - Piperacillin/tazobactem
  - If hypotensive and unwell-appearing, add tobramycin
  - If AML or high dose cytarabine (increased risk for staph sepsis); add vancomycin
  - If GI symptoms, add flagyl

BACK TO OUR CASE

- Red flags identified on history and physical exam:
  - Weight loss (subjective), fatigue
  - Noticeable pallor → CBC later showed anemia
  - New onset epistaxis (no prior history) → CBC later showed thrombocytopenia
  - Fever – although not prolonged, associated with ?sore throat at the time

BACK TO THE CASE

26-Feb-16 03:50	Fibrinogen		
Fibrinogen		2.81	[1.70-3.50 g/L]
26-Feb-16 03:50	**INR**		
INR		1.10	[0.86-1.24]
26-Feb-16 03:50	**PTT**		
PTT		18.5 ↓	[20.0-34.0 secs]
26-Feb-16 03:50	**CBC AND DIFFERENTIAL**		
WBC To be verified.		28.5 ↑	[4.7-13.5 10|9/L]
RBC		2.97 ↓	[3.70-5.00 10|12/L]
Hgb		84 ↓	[105-135 g/L]
Hct		0.242 ↓	[0.310-0.398 L/L]
MCV		81.5	[71.0-85.0 fL]
MCH		28.3	[23.7-29.5 pg]
MCHC		347	[320-360 g/L]
RDW		14.6	[12.0-15.1 %]
PLT To be verified.		23 ↓↓	[150-450 10|9/L]
MPV Not available.		*	[9.0-14.0 fL]
Immature Platelet Fraction		10	[%]
Immature Reticulocyte Fraction		14.8	[8.4-21.7 %]
Retic Hemoglobin Equilvalent		40.0	[pg]
Neutrophils		0.9 ↓	[1.5-8.5 10|9/L]
Lymphocytes		7.7 ↑	[1.0-5.5 10|9/L]
Monocytes		0.3	[0.1-1.0 10|9/L]
Blasts		12.5 ↑↑	[<=0.0 10|9/L]
Retic		17 ↓	[22-92 10|9/L]
Bands		0.3	[0.2-0.5 10|9/L]
Smudge Cells		6.8	[10|9/L]

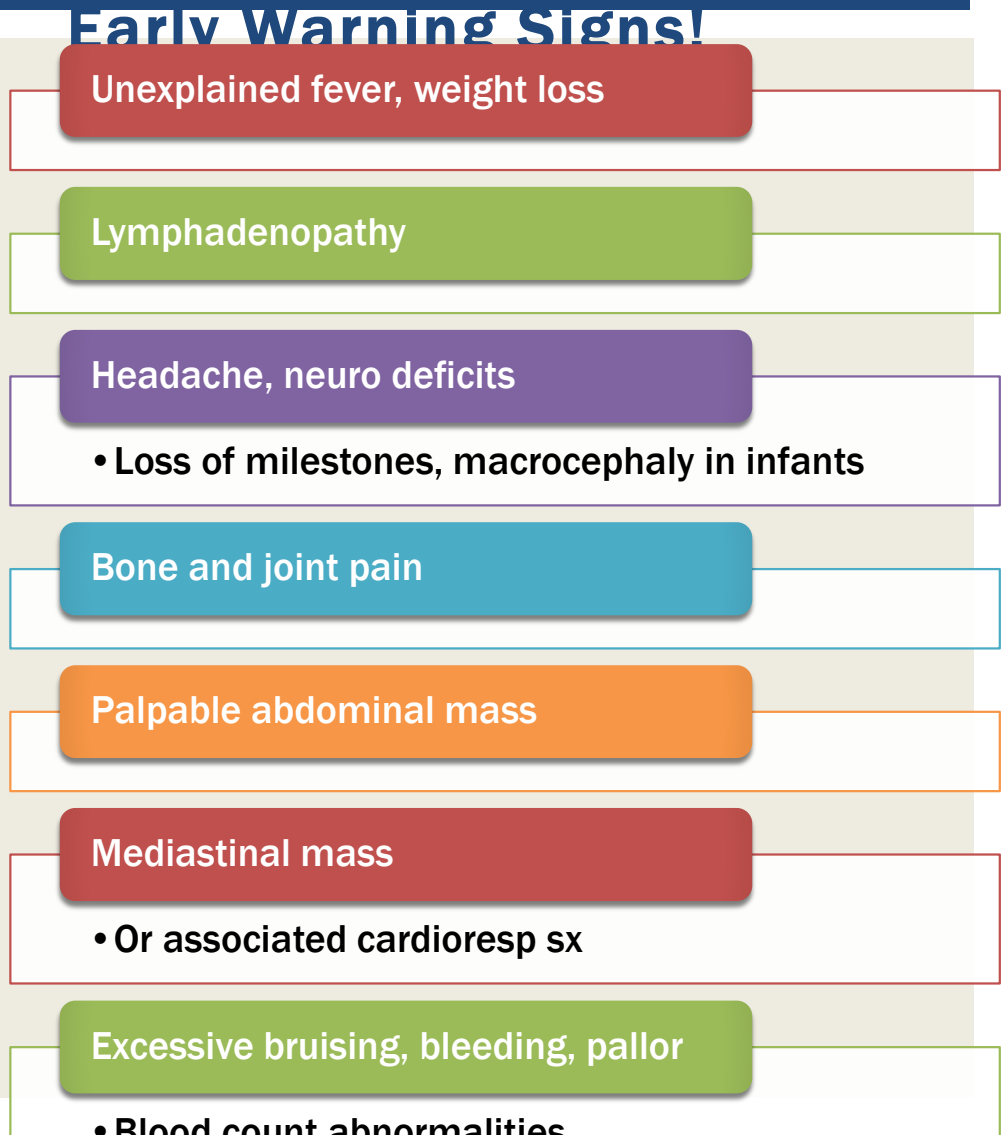
BACK TO THE CASE

26-Feb-16 09:20	BM Aspirate	Resulted
BM Reason for Procedure	4 year old female with pancytopenia and peripheral blasts	
BM Site	Right posterior iliac crest	
BM Tech Comment	*	
BM Peripheral Blood Morphology	Multilineage cytopenias with the presence of circulating blast cells. Blast cells are small to medium in size with scant cytoplasm. Auer rods are not visualized.	
BM Fragments	Multiple fragments are present.	
BM Cellularity	Markedly hypercellular fragments and cell trails.	
BM Erythropoiesis	Markedly decreased in number.	
BM Myelopoisesis	Markedly decreased in number. Blasts 90-95%.	
BM Megakaryopoiesis	Markedly decreased in number.	
BM Interpretation	This is a hypercellular aspirate specimen with almost complete absence of normal haematopoiesis. There is a blast population that makes up 90-95% of the differential count. Blasts are small to medium in size with scant cytoplasm. Occasional vacuolization is noted. Auer rods are not visualized. Flow immunophenotyping confirms that the blasts are B-lymphoblasts. Please see flow report for full details. Diagnosis: B-lymphoblastic leukemia (pre-B-ALL). Initial diagnostic evaluation. Reported by Dr Elaine Leung, MD, FRCPC, Haematopathologist.	
BM Neutrophils	0.00 ↓	[0.07-0.30 L/L]
BM Bands	0.01 ↓	[0.12-0.34 L/L]
BM Metamyelocytes	0.00 ↓	[0.04-0.15 L/L]
BM Myelocytes	0.00 ↓	[0.03-0.15 L/L]
BM Blasts	0.94 ↑	[0.00-0.04 L/L]
BM Lymphocytes	0.01 ↓	[0.03-0.17 L/L]
BM NRBC	0.03 ↓	[0.05-0.20 L/L]
BM Aspirate	Adequate for interpretation	

- Diagnosed with pre-B ALL after BMA
- Started on induction chemotherapy during admission

SUMMARY

- Early symptoms for childhood cancers nonspecific, often similar to common conditions
- High level of suspicion needed by primary care practitioner
  - Early referral to pediatric oncology improves prognosis, reduces complications



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3. Kaatsch, P. Epidemiology of childhood cancer. Cancer Treat Rev 2010, 36(4): 277-285.
4. Neville, KA and Steuber CP. Table 1: Most common malignancies in infants, children, and adolescents. Clinical assessment of the child with suspected cancer. UptoDate 2016.
5. Fragkandrea, I., Nixon, JA., Panagopoulou, P., Signs and symptoms of childhood cancer: a guide for early recognition. AAFP 2013, 88(3): 185-192.
6. Oncology Emergencies (CHEO Pediatric Resident Academic Half Day), presented by Dr. Donna Johnston.

Special thanks to Dr. Donna Johnston for her input in reviewing this presentation.

Questions or Comments?

Video-conferencers:
Unmute your system to ask a question

Webcasters:
Type your question

Thank you!

for participating in today's

Pediatric Telehealth Rounds

Join us next time:

Suspected Sexual Assault
Brigitte Richard & Dr. Louise Murray

April 15, 2016

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