Constipation or Cancer?
Diagnostic Dilemmas in Childhood Malignancies

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• No conflicts of interest to disclose.

Learning Objectives
1. Describe the clinical presentation of the most common pediatric cancers.
2. Recognize suspicious laboratory findings indicative of a possible cancer diagnosis.
3. Identify patients in the primary care office needing emergent oncology evaluation.
2 year old girl with cough...

- 3 months: persistent cough following an upper respiratory illness
  - Allergy: antihistamine
  - Asthma: albuterol, inhaled glucocorticoid
  - GERD: ranitidine

- 6 months: pulmonology
  - Chronic rhinitis and sinusitis: antibiotics, intranasal steroids

- 9 months: ENT
  - Upper airway obstruction with OSA: adenoidectomy, tympanostomy tubes

- 11 months: GI
  - Esophageal motor dysfunction or EE: PPI and upper endoscopy

- 12 months: PCP
  - Progressively worsening cough and breathing
  - Oxygen saturation: 82%

- Emergency Room
  - Respiratory distress
  - Altered consciousness
  - Facial neurologic findings:
    - Nystagmus
    - Asymmetric face and facial weakness
    - Leftward tongue deviation
    - Left extremity weakness

See the Forest...

- Chronic cough:
  - Choking on solids
  - Drooling
  - Pooling secretions
  - Sleep on pillows
  - Cough ↑ sleeping
  - Cough ↑ anesthesia
  - Gagging on purees
  - Balance issues
  - Difficulty sitting upright
  - "Drunken" walking
  - Left eye droop
Diagnosing Childhood Cancer

- Pediatric cancer is rare.
- Symptoms are non-specific and vague.
- Childhood malignancies are highly variable: heterogenous presentations.
- Symptom onset is gradual: delayed diagnosis.

Childhood Cancer

- Rare Disease:
  - 1% of all cancer.
  - 15,000 new cases per year.
  - 10,000 age 0-14
  - 5,500 age 15-19
  - Incidence - 1 in 285 children.
  - 0.25% chance of cancer before 20.
  - 80% patients: long-term survivors.

Childhood Cancer in Primary Care

- Identifying pediatric cancer: once-in-a-career event.
- Feltbower et al. Brit J Cancer, 2004:
  - Incidence rates: PCPs in geographic regions.
  - 1 cancer diagnosis per PCP every 20 years.
- Chen and Mullen. J Pediat Hematol Oncol, 2017:
Cancer Symptoms

- Earliest cancer symptoms: vague.
- 363 pediatric cancer pts: PCP surveyed.
- 72% symptoms: general and unspecified.
- 20% symptoms: “alarm” symptoms
- Case-control study: 1267 cases
- 27% cases: “alert” symptoms
- 3 months prior to diagnosis.

Childhood Cancer: Epidemiology

- Age-adjusted age-specific cancer incidence rates for patients aged 0-19 years (1998-2012)
- Leukemia: 3 weeks
- CNS: 9 weeks
- Solid Tumors: 12 weeks

Delays in Diagnosis
Delays in Diagnosis

• >100 studies of diagnostic delays in childhood cancer: conflicting results
• Prognosis may be impacted.
• Psychological well-being will be impacted.

Leukemia
• Tumor lysis and ↑ WBC
• ↑ CNS involvement

Lymphoma
• Tumor lysis
• Mediastinal mass, SVC syndrome
• Sarcoma
• Mediastinal mass or lung lesion

Brain Tumors
• ↑ Intracranial pressure
• Neurological symptoms

Diagnostic Error

<table>
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<tr>
<th>Diagnostic Error</th>
<th>Causes</th>
<th>No. of Patients</th>
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<tbody>
<tr>
<td>Diagnosed in acute</td>
<td>Leukemia</td>
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<tr>
<td>Diagnosed in cancer</td>
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<tr>
<td>Diagnosed in remission</td>
<td>Leukemia, lymphoma</td>
<td>6</td>
</tr>
<tr>
<td>Diagnosed in chronic</td>
<td>Leukemia, lymphoma</td>
<td>6</td>
</tr>
<tr>
<td>Diagnosed in relapse</td>
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</tr>
<tr>
<td>Diagnosed in secondary</td>
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</tr>
<tr>
<td>Diagnosed in indolent</td>
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</tr>
<tr>
<td>Diagnosed in advanced</td>
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<td>4</td>
</tr>
<tr>
<td>Diagnosed in resistant</td>
<td>Leukemia, lymphoma</td>
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Diagnosing Childhood Cancer

• Pediatric cancer is rare.
• Primary care physicians almost always consulted first.
• Symptoms are non-specific and vague.
• Red flag symptoms → high index of suspicion

• Childhood malignancies are variable disease processes with heterogeneous presentations.
• Parental concerns and frequent visits to primary care are common.

• Symptom onset is gradual and diagnosis is often delayed.
• You have time to make the diagnosis without compromising safety.
A Case of Fatigue

- 11 year old girl with no prior medical hx seen for sick visit:
  - Right foot pain several weeks, gradually worsening.
  - "Low energy" → tires easily during dance class.

- Sick visit #2
  - Foot pain not improved
  - "Flew all of the time" → putting herself to bed

- Sick visit #3
  - Right foot pain increased and swollen
  - Tongue and palor

- Sports Medicine
  - MRI of right foot

A Case of Fatigue

Acute Lymphoblastic Leukemia

- 4% Neutrophils
- 6% Bands
- 60% Lymphocytes
- 2% Monocytes
- 28% Other cells

Childhood Leukemia

- Acute Leukemia
  - ALL: 75%
    - T cell
    - Pre B cell
    - MLL
  - AML: 20%
    - M1
  - Rare: 5%
    - Undifferentiated

- Chronic Leukemia
  - Chronic

Acute Leukemia

Chronic Leukemia

Incidence:

- ALL: 2500-3000 cases per year
- AML: 500 cases per year

- 3-4 ALL cases per 100,000 children

Peak Incidence:

- ALL: 3-5 years old
- AML: peaks in infancy and adolescence
Symptoms of Acute Leukemia

**Marrow Replacement**
- Fever/Infection: 60%
- Petechiae/Bleeding: 50%
- Pallor: 40-50%
- Fatigue: 40-50%
- Bone pain: 25%

**Lymphoid Infiltration**
- Hepatomegaly: 68%
- Splenomegaly: 63%
- Lymphadenopathy: 50%

**Other**
- Malaise
- Weight loss and anorexia
- Headache from CNS involvement
- Mediastinal mass

**COMBINATION OF SYMPTOMS RAISE SUSPICION FOR LEUKEMIA CONSIDER CBC AND SMEAR**

**Lab Abnormalities in Acute Leukemia**

- **WBC Count**
  - 80-90%: leukocytosis and leukopenia
  - 50% WBC >20,000
  - 30-40% WBC <5,000
  - **blasts may not be seen**

- **RBCs and Platelets**
  - 90%: anemia and/or thrombocytopenia
  - 50% of ALL: Hgb <7.5
  - 75% of ALL: Plts <150
  - 80% of AML: Plts <100

- **Peripheral smear**
  - Immature WBC's: Blasts, Metamyelocytes, Promyelocytes, Plasmacytoids
  - Caution: atypical lymphocytes

- **Other labs**
  - ↑ LDH
  - ↑ uric acid
  - ↑K, ↑Ph, ↓Ca (tumor lysis)
  - Renal or hepatic dysfunction
  - Disseminated intravascular coagulation

1. ↑ ↓ WBC with ↓ RBC or ↓ Plts.
2. Immature WBC's.
3. Lack of obvious infectious cause.
4. Associated symptoms.

**Constitutional Symptoms**

- Non-specific symptoms that mimic benign childhood illnesses:
  - 85% of pediatric cancer

- **“B Symptoms”** → Hodgkin lymphoma
  - Fever >38°C x 3 days
  - Weight loss ≥10% in 6 months
  - Drenching night sweats

- Others: pallor, malaise, fatigue, anorexia, failure to thrive, recurrent infection, growing pains, etc.

1. Multiple Constitutional Symptoms
2. Constitutional Symptoms + Labs
3. Constitutional Symptoms + Exam
4. Constitutional Symptoms + Multiple Visits
A Case of Fever

• 19 month old boy previously healthy seen for sick visit with acute fever:
  * Diagnosed with acute otitis media → antibiotics

• ER visit 5 days later for persistent fever.
  * No AOM on exam → viral illness → home

• ER visit 5 days after that. Fevers unchanged.
  * Unwillingness to bear weight.
  * “I think he’s having pain.”

A Case of Fever

• Returned to primary care physician.
  * 5 weeks of daily fever.
  * Refusing to walk and very irritable.
  * Abdomen full → constipation

• Cardiology 2 days later.
  * Echocardiogram...

Pediatric Abdominal Masses

- Benign
  * Hydronephrosis
  * Polycystic kidney
  * Adrenal hemorrhage
  * Pyelonephritis
  * Cholesteatoma
  * Ovarian cyst
  * Intestinal duplication
  * Constipation

- Malignant
  * Neuroblastoma
  * Wilms Tumor
  * Lymphoma
  * Soft Tissue Sarcoma
  * Germ Cell Tumor
  * Ewing Sarcoma
  * Other renal tumor
  * Hepatorenal sarcoma

- Neuroblastoma
  * Peak 0-2 years
  * Fever, bone pain, wt loss
  * Painful mass

- Wilms
  * Peak 2-3 years
  * No systemic symptoms
  * Painless mass
  * Incidental finding

ANY PALPABLE ABDOMINAL MASS REQUIRES ULTRASOUND
Neuroblastoma

- Most common extracranial solid tumor in children
  - 650 cases per year
  - 8% pediatric cancer
  - 15% pediatric cancer death
- Embryonal tumor of sympathetic nervous system.
  - 50% metastasis
- Paraneoplastic Syndromes:
  - Opsoclonus-Myoclonus-Ataxia
  - Kerner-Morrison Syndrome

Fever

- Prolonged fever is common at cancer diagnosis:
  - Leukemia
  - Lymphoma
  - Hodgkin lymphoma
  - Anaplastic Large Cell Lymphoma
  - Neuroblastoma
  - Ewing sarcoma
  - Langerhan’s Cell Histiocytosis
  - Rhabdomyosarcoma
- Fever of Unknown Origin
  - Infectious or not unknown
  - 9-9% due to occult malignancy

A Case of Lymphadenopathy

- 16 yo male with ASD/OCD, eczema: eval by ENT for right neck swelling:
  - Right supraclavicular lymph node palpated and tender
  - Sent home on ciprofloxacin for presumed lymphadenitis
- Returned to ENT 2 weeks later:
  - Unchanged right supraclavicular LN and overlying eczema
  - Started on prednisone
- Follow-up in 2 weeks:
  - Eczema improved
  - Supraclavicular LN slightly larger
  - Right anterior cervical LAD

ESR 84
RR 98 SVR Trap
A Case of Lymphadenopathy

- Ultrasound-guided lymph node biopsy 3 weeks later.
- Pathology results pending.
- Presents to ER with increased neck swelling 1 week later:

```
11.1 35.2
ESR 134
LDH 560
Uric Acid 9.2
```

Lymph Nodes in Children

- Most children → small palpable LN's
  - 46% well child checks
  - 64% childhood sick visits
- Palpable lymph nodes only rarely indicate underlying cancer:
  - Fijten, Blijham, J Fam Pract, 1988: 2,556 pts with unexplained LAD
  - 10% referred to subspecialist
  - 3.2% lymph node biopsy
  - 1.1% malignancy
  - 0.4% <40 yo malignancy
- Prevalence of cancer in LN biopsies:
  - 11-29% pediatric referral centers

Lymph Node Exam

- **Size**
  - Enlarged >10 mm
  - Exceptions:
    - Epitrochlear >5 mm
    - Inguinal >15 mm
- **Characteristics**
  - Reassuring:
    - Tender, Mobile, Soft/Fluctuant, Warmth/Erythema
  - Worrisome:
    - Nontender, Matted, Firm/Rubbery, Nonsuppurative
- **Location**
  - Localized versus Generalized
    - Ipsilateral
    - Ipsilateral:
      - Neck
      - Axillary
      - Supraclavicular
    - Contralateral:
      - Aortic nodes
    - Posterior auricular
    - Epitrochlear
    - Inguinal
      - Location
      - Associated systemic findings:
        - Hepatomegaly
        - Splenomegaly
        - Rash, Bruising
        - Mucous membrane involvement
Diagnostic Algorithm

Lymphadenopathy

- **Indications for Biopsy**
  - Abnormal CBC or CXR
  - Constitutional symptoms
  - Concerning exam findings
  - Asymptomatic node >2.5 cm
  - Increasing size >4 weeks
  - Stable size >6 weeks

- **Pearls of Wisdom**
  - Watchful waiting up to 4 weeks
  - Antibiotic course appropriate*
  - CBC, ESR, Chest X-ray at 4 weeks
  - Ultrasound can be very helpful
  - Always avoid steroid therapy!!!
  - Excisional (not needle) biopsy

EBV and Lymphoma

- **Infectious Mononucleosis and Hodgkin Lymphoma can be clinically indistinguishable:**
  - Constitutional symptoms: fever, weight loss, anorexia, night sweats
  - Generalized lymphadenopathy: matted and hard
  - Splenomegaly

- **Strong association between EBV infection and development of HL**
  - 20-50% classical HL tumors are EBV positive
  - 1:2000 patients with infectious mono will develop HL
  - EBV DNA detected in plasma of HL patients

*POSITIVE EBV TESTING DOES NOT RULE OUT LYMPHOMA
A Case of Vomiting

- 2.5 yo female with no PMHx presents as a sick visit:
  - "Vomiting on and off for 1-2 months"
  - Emesis typically overnight; no diarrhea or fever
  - Recurrent viral infections

- Returned to primary care 1 week later:
  - Daily vomiting, always between 3-6AM
  - No abdominal pain or nausea; possibly decreased bowel habits

- Returns again the following week: no improvement.
  - Eating well without nausea
  - Vomiting 3 times per night

A Case of Vomiting

Childhood Brain Tumors

<table>
<thead>
<tr>
<th>Low Grade</th>
<th>High Grade</th>
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<tbody>
<tr>
<td>Surgery alone</td>
<td>Surgery and Radiation and Chemotherapy</td>
</tr>
<tr>
<td>Observation</td>
<td></td>
</tr>
<tr>
<td>Low-dose chemotherapy</td>
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Favorable Prognosis

- Pilocytic Astrocytoma
- Ganglioglioma
- Oligodendroglioma

Poor Prognosis

- Medulloblastoma
- Ependymoma
- Glialblastosoma

Germ Cell Tumors

- Craniopharyngioma
- Medulloblastoma
- Ependymoma
- Glioblastoma

Favorable Prognosis

- Surgery alone or Observation or Low-dose chemotherapy

Poor Prognosis

- Surgery and Radiation and Chemotherapy
Childhood Brain Tumors

- Incidence
  - 5.4 per 100,000 population.
  - 4300 new diagnoses per year.
- Prevalence
  - 2.5 per 100,000 population.
  - 28,000 children in US

Outcomes

- 65-70% overall survival at 5 years
- Leading cause of cancer-related deaths

Survival at a Cost:
  - Highest cause of morbidity

Diagnosing Brain Tumors

- Everyone thinks they have a brain tumor.
- Patients present with relatively common problems:
  - Headaches
    - 40-50% elementary-aged children
    - 60-80% high school-aged children
  - Seizures
    - 2-5% of children → febrile seizures
    - 25,000-40,000 children with unprovoked seizures each year in the US

Decision to image is challenging:

- Symptom onset is subtle and gradual.
- Parents of brain tumor patients: diagnosis only reached after repeated insistence that the child was unwell.

Brain Tumor Symptoms

- Hydrocephalus
  - Headache and vomiting
    - Overnight or early morning
  - Gait or truncal ataxia
  - Papilledema
  - Sunsetting eyes
- Infants nonspecific
  - Increasing head circumference
  - Bulging fontanelles
  - Seizures → frontal/temporal lobes
  - Visual disturbance → optic pathway
- Endocrinopathies → sella
  - Diabetes insipidus
  - Delayed or precocious puberty
  - Diabetes insipidus
- Cranial nerve palsies → brainstem
  - Hemiparesis → parietal lobe, spine, brain stem
  - Change in behavior school performance → ???
Headaches and Vomiting

- Brain tumors rarely cause headache.
- Probability of brain tumor:
  - 0.01% chronic HA and no neuro sx
  - 0.4% migraine and no neuro sx
  - 4% HA >6 mo and neuro sx
- When brain tumors do cause headache:
  - Hydrocephalus → Vomiting
  - 95% with neurologic sx
  - 94% progressive sx within 4 mo
- When To Be Worried
  - Nocturnal HA
  - Wakes from sleep
  - Upon awakening
  - Associated vomiting
  - HA during day with vomiting
  - Vomiting
  - Nocturnal or upon awakening
  - New onset of sx
  - New onset HA >4 weeks

A Case of Knee Pain...

- 13 year old male seen by his PCP for routine well child visit:
  - March: Baseball Injury
  - Intermittent R knee pain
  - April: Normal exam
  - May: Sick Visit
  - June: ER Visit
  - July: 2nd ER Visit

Bone Pain in Children

Infection/Related
- Septic Arthritis
- Osteomyelitis
- Reactive Arthritis
- Lyme Disease
- Tark Sprains

Trauma
- Stress fracture
- Soft tissue injury
- Osgood-Schlatter
- Hypermobility

Inflammatory
- JA
- SJG
- HSP

Neuropathic
- Growing Pains
- Fibromyalgia
- Reflex sympathetic dystrophy
- Restless leg

Metabolic
- Rickets
- Scurvy
- Hypervitaminosis A
- Gaucher’s
- RTA

Malignancy
- Osteosarcoma
- Ewing sarcoma
- Leukemia
- Lymphoma
- Neuroblastoma

Orthopedic
- Bone tumors
- Legg-Calve-Perthe
- OCD
- Patellar tendinitis
- Patellar instability

Infectious
- Septic arthritis
- Osteomyelitis
- Lyme disease

Inflammatory
- JIA
- SLE
- HSP

Noninflammatory
- Growing Pains
- Fibromyalgia
- Reflex sympathetic dystrophy
- Restless leg
Bone Pain in Children

- Acute Leukemia
  - 20-30% present with pain
  - Systemic symptoms
  - Abrupt onset

- Malignant Bone Tumors:
  - 80-90% present with pain:
    - Pain with strain 78%
    - Pain at night 20%
    - Pain with mass 37%
    - Pain with fracture 5%

- Evaluation for cancer:
  - Abrupt onset/systemic symptoms
  - Persistent pain
  - Associated swelling
  - Nocturnal pain

Bone Cancer Symptom Timeline

Pain at Night

Growing Pains
- Age 3-12
- Bilateral
- Episodic
- Resolves by morning
- Daytime symptoms: do not restrict activity
- Relieved with massage/heat
- Abdominal pain and headaches
- Normal exam

Juvenile Idiopathic Arthritis
- Distinguishing Acute Leukemia:
  - Caution rash, arthritis, ANA
  - Obtain CBC, cytopenia

- Recognizing atypical JIA:
  - Night pain
  - Severe pain
  - Non-joint pain
  - Minimal arthritis
  - Systemic symptoms > arthritis

Evaluating Bony Lesions

- Laboratory Studies:
  - CBC
  - Alkaline Phosphatase
  - LDH
  - ESR

- Imaging
  - Radiographs
  - +/- MRI
Take Home Points

• Diagnosing childhood cancer is hard.
  ▶ Rare and symptoms are vague.

• The diagnosis of childhood cancer is almost never done in a single visit.
  ▶ Delayed diagnosis often does NOT impact outcome.

• See the forest for the trees....
  ▶ Overall well-being and associated symptoms > focusing on single chief complaint.

• Red flag symptoms → raise index of suspicion.

Red Flag Symptoms

• Persistent or multiple constitutional symptoms → CBC with diff + smear.

• CBC abnormalities + symptoms + no obvious infection → acute leukemia.

• Any palpable abdominal mass → ultrasound.

• Recurrent fever with no clear infectious source → consider malignancy.

• Lymphadenopathy → exam is key (EBV can still be lymphoma).

• Headache and/or vomiting at night or early morning is very concerning.

References


