Solid tumors

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CASE 1

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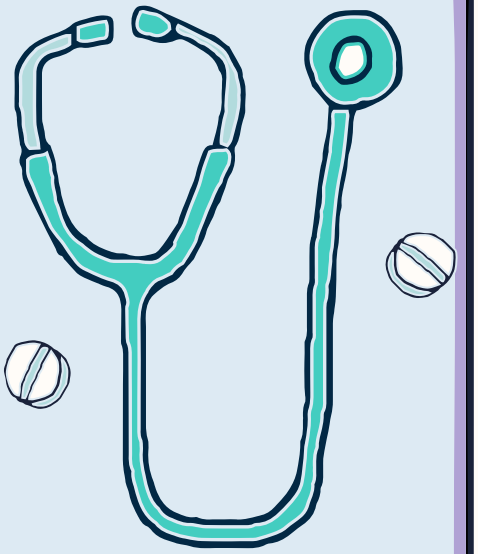
HISTORY

A **15**-year-old **female** presents to the office complaining of dull right **thigh pain** for the past **2 months**. She denies any trauma or inciting events over that time. The pain was **initially present only while walking** and after other physical activities but has progressed and **is present at rest**. It now **disrupts her sleep at night**. She is otherwise healthy and **denies any fevers, chills, weight loss, or night sweats**.

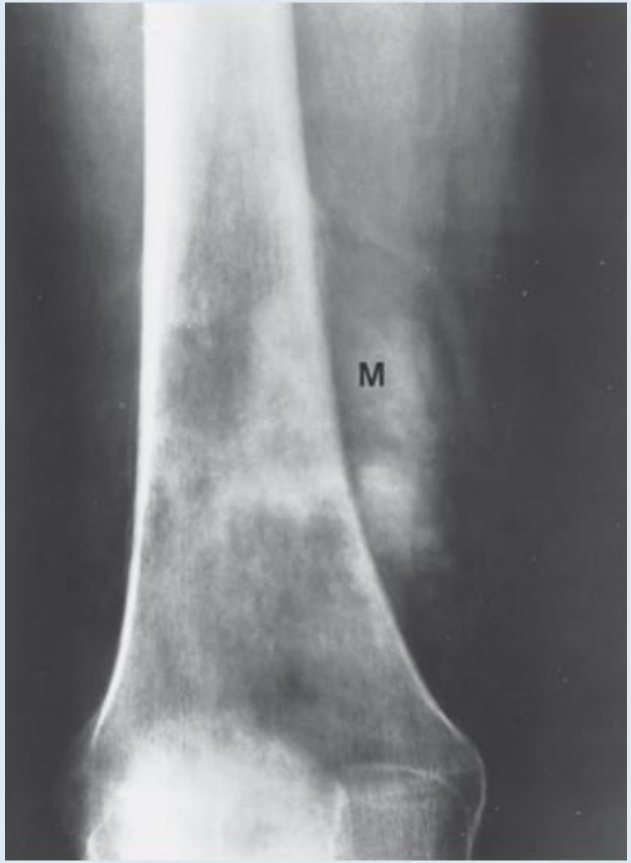
PHYSICAL EXAMINATION

- On physical exam, her right lower extremity is neurovascularly intact. Her knee has full range of motion, and there is no warmth or erythema.
- However, you do note mild **swelling of her distal thigh** and on palpation appreciate a **mass in that region.**
- **MASS**: tender, ill-defined margin, smooth surface, hard, not movable, fixed to underlying tissue, overlying skin is free

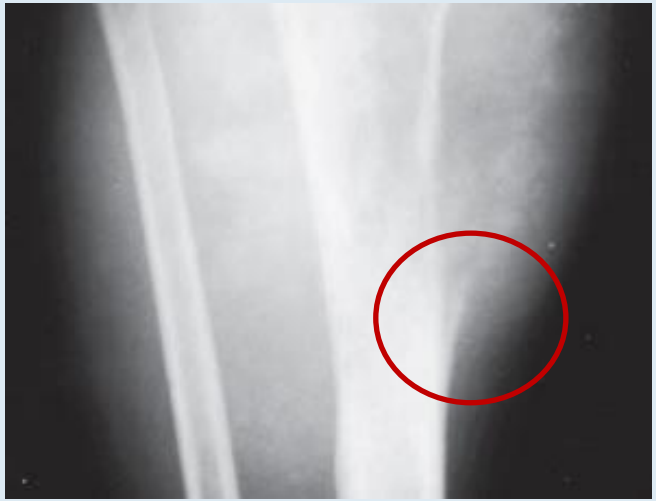


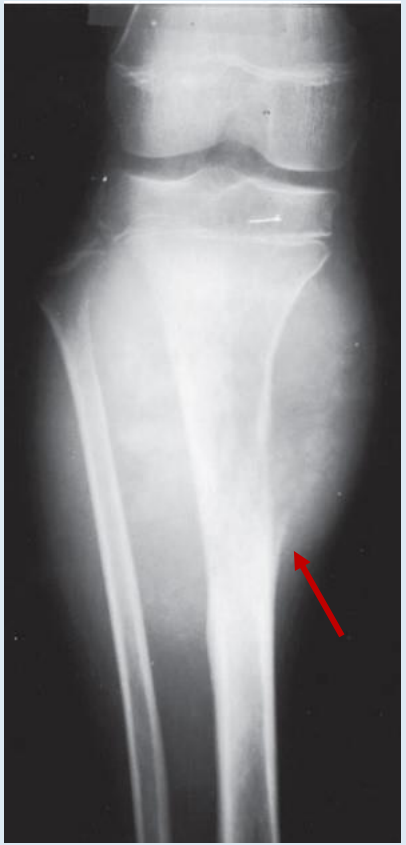
X-RAY

AP view of the distal femur. Many of the radiographic features of this osteosarcoma mark it as a malignant tumor. The abnormal area of mottled lucent and sclerotic tumor in the metaphysis fades gradually into the shadows of surrounding normal bone. **It is difficult to see where the tumor begins and ends**; **there is a large soft-tissue mass adjacent to the bone** (M). The periosteum has been unable to maintain a shell of mineralized new bone around this mass. The sclerotic areas within the bone and the mineralized portions of the soft-tissue mass both have a relatively amorphous, smudged appearance that is seen with calcified osteoid matrix



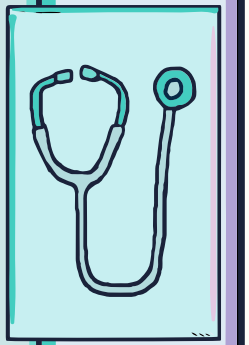
Codman's triangle





What's your diagnosis?

OSTEOSARCOMA



- **Osteosarcoma** is the most common bone sarcoma
- Peak in second decade of life **(13-16)**
- most commonly seen at sites **of rapid bone turnover**, such as the **distal femur > proximal tibia > proximal humerus > and proximal femur > other bones**
- Most cases are **sporadic**. However, those that retinoblastoma tumor suppressor gene **(RB1)** or who have Li-Fraumeni syndrome **(p53 gene)** are predisposed

- A common presenting complaint is **new-onset pain over several months** duration; it may occur **at rest, disrupt sleep**, or only occur after physical activity.
- A patient with an osteosarcoma may also present with a **palpable mass** in the extremity that is painful.
- Symptoms such as fevers, chills, weight loss, and fatigue are late signs of disease.

- An osteosarcoma classically arises from the **metaphyseal region** of a bone and appears as a mixed sclerotic and lytic lesion that can infiltrate bone surrounding cortex, causing a **periosteal reaction** and soft **tissue mass**. A **Codman triangle** may be seen on radiographs

What are the next steps in the workup?

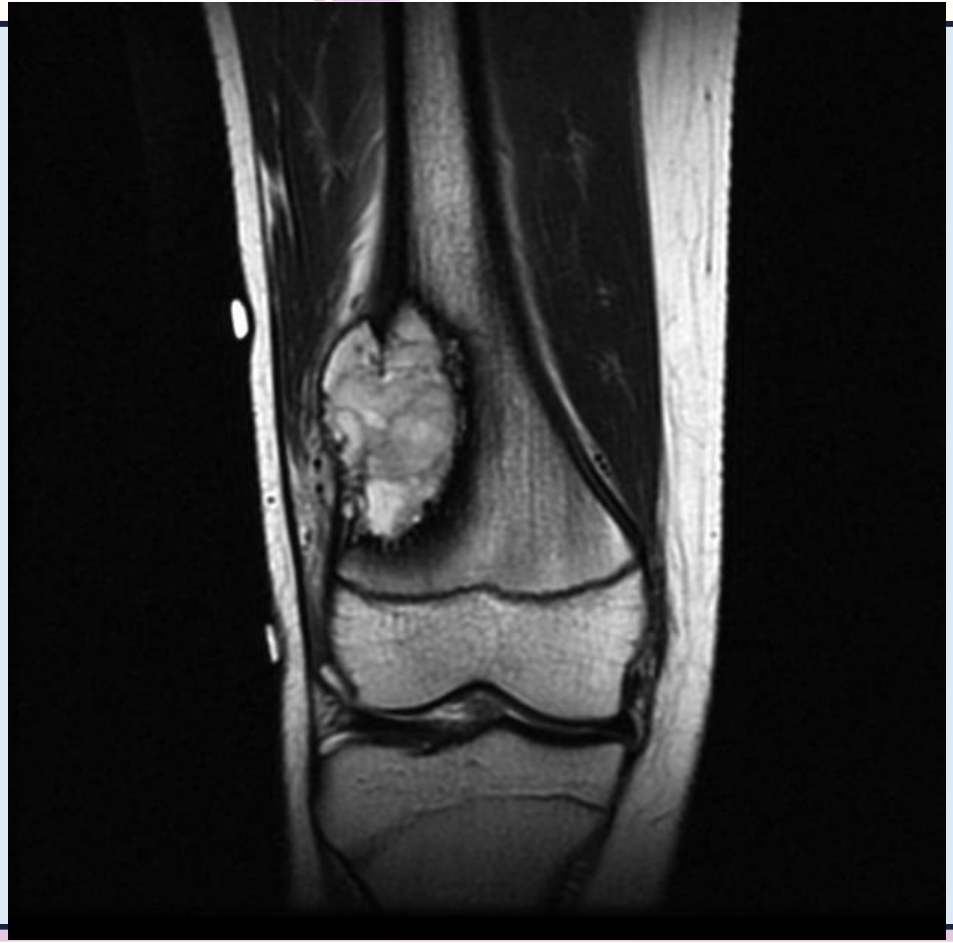
MRI

Plain radiographs concerning for a malignant bone lesion require advanced imaging, such as an MRI, to evaluate for **surrounding soft tissue, neurovascular, and bone marrow involvement,** as well as **skip lesions**, which represent discontinuous metastases.

BIOPSY

A biopsy of the lesion is required when the imaging, examination, and history are consistent with a pathologic process; it is the **only definitive** means of determining whether a tumor is benign or malignant.

MRI



What are the next steps in the workup?

LABS

Laboratory testing is not diagnostic for osteosarcoma. Before initiation of chemotherapy, laboratory values (CBC, basic metabolic profile, LFT, KFT) must be obtained to provide a **baseline** assessment of organ function. **Elevates ALP, LDH are poor prognostic factors**.

Chest CT & Bone scan

Chest CT and bone scan evaluate for **metastatic disease**, which is the most important prognostic and staging factor in osteosarcoma.

What is the treatment approach?

Radiation is not used in the treatment of osteosarcoma

Neoadjuvant chemotherapy

Wide margin surgical resection

Postoperative chemotherapy

- Fortunately, approximately **90%** of patients with osteosarcoma are able to undergo **limb salvage procedures** and do not require amputation.
- The excised segment of bone may be replaced with a prosthesis and/or allograft

PROGNOSIS

- The overall **5-year** survival rates of patients with osteosarcoma are **60% to 80%.**
- With the initiation of neoadjuvant chemotherapy protocols, 5-year survival rates are almost 80% in patients with nonmetastatic disease and 10% to 20% in patients with metastatic disease.

- **Poor prognostic factors**

a) elevated alkaline phosphatase and lactate dehydrogenase
b) metastatic disease at diagnosis
c) poor response to chemotherapy (defined as < 90% necrosis of resected tumor)
d) pathologic fracture.

CASE 2

A 2-year-old boy presented to the clinic with morning **headaches** and Intermittent **emesis** for one month duration , Physical examination revealed **broad-based gait**, difficulty with heel-to-toe walking ,Head titubation (bobbing) and nystagmus

What is the next step in evaluation?

Investigations ???

What is the most likely diagnosis?

???

What is the best management for this condition?

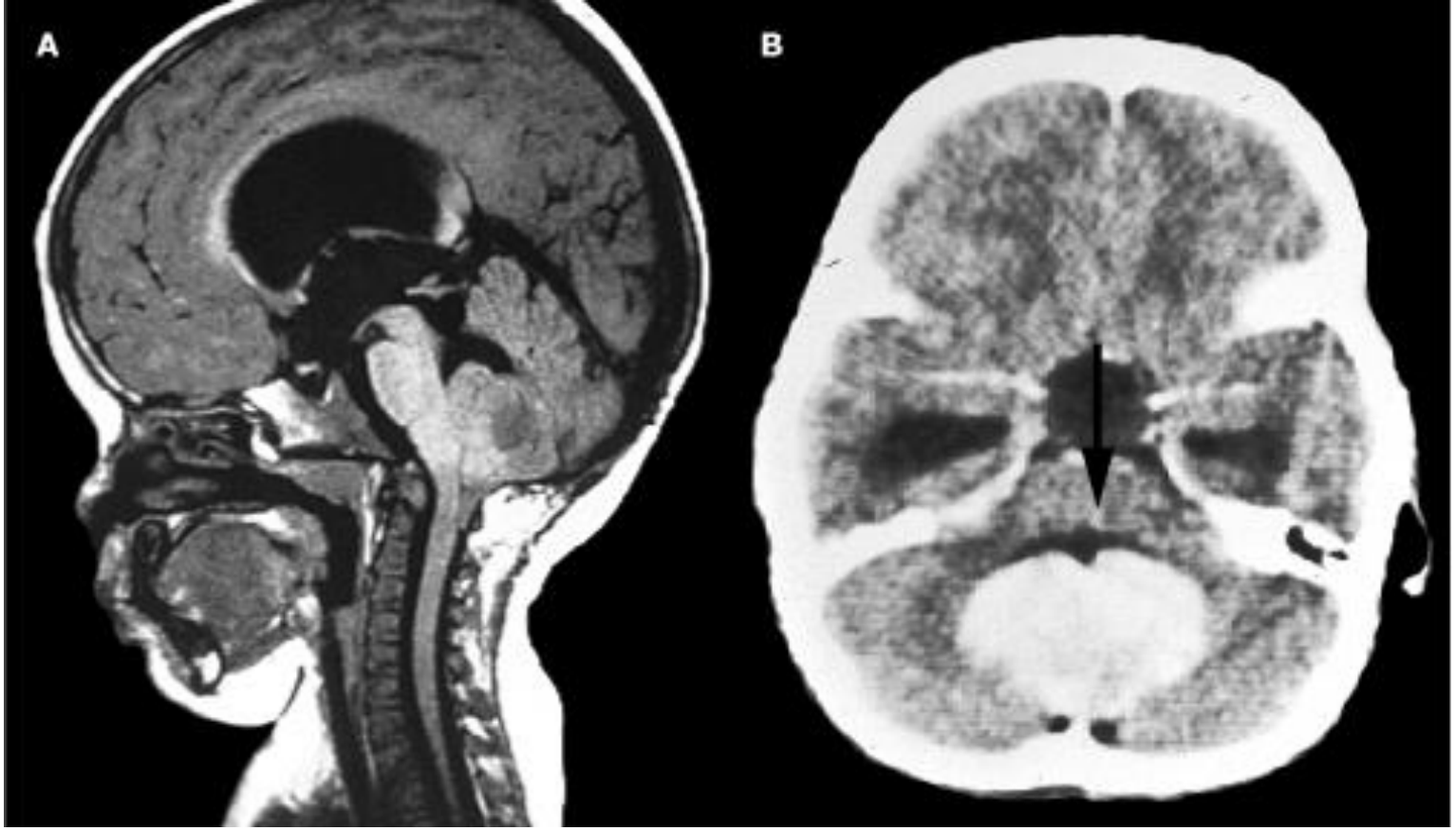
???

Laboratory Studies

- Complete blood cell (CBC) count
- Electrolytes
- Liver, and renal function tests

Baseline thyroid function studies viral titers are also recommended

Imaging ???



(A) MRI sagittal image of a posterior fossa mass causing compression and dilatation of the third and lateral ventricles.

(B) CT with contrast: Axial image that demonstrates a large posterior fossa mass causing compression of the fourth ventricle (arrow) and dilation of the temporal horns.

Neuroimaging

CT scan

The classic CT finding is a ***hyperdense mass*** on an unenhanced study that markedly enhances after the injection of contrast medium

contrast-enhancing midline or paramedian cerebellar tumor that often compresses the fourth ventricle

Head MRI with and without contrast

Spinal MRI

Detection of ***spinal cord metastasis***.

Neuroimaging

CT scanning

CT scan of the brain is commonly used during **initial evaluation** of patients with neurologic symptoms. In patients with medulloblastoma, CT scan of the head with and without contrast usually shows ***a solid mass in the 4th ventricle with prominent hydrocephalus*** in most patients. The vast majority (95%) of medulloblastoma are contrast-enhancing.

MRI

Head and spinal MRI with and without contrast should be performed in all patients with CT or clinical findings consistent with medulloblastoma. MRI better demonstrates the anatomic origin and extent of tumor . More than 90% of medulloblastoma tumors enhance with contrast. **Contrast is essential to detect CSF dissemination**.

Preoperative and postoperative MRI is required for detection and measurement of residual disease following surgical resection. **Postoperative MRI** evaluation should be performed **within 72 hours** of surgery to delineate residual tumor from the postsurgical inflammatory changes that are visualized on MRI at this time.

Spinal MRI is the most sensitive method available for detection of ***spinal cord metastasis***.

Cerebrospinal fluid analysis

— WHY ?
— Findings ??

positive cytology >>> Elevated protein and a mild pleocytosis , but these findings are nonspecific.
A positive lumbar CSF cytology either pre- or postoperatively predicts for an increased rate of relapse and poor outcome .
Negative cytology >>> does not exclude a more advanced stage of disease

Confirm the diagnosis ??

A diagnosis of medulloblastoma requires **histopathologic confirmation** at the time of surgical resection. Biopsies are not routinely performed in patients suspected of having a medulloblastoma by imaging, because maximal safe resection is an integral part of the management and prognosis of medulloblastoma as well as other posterior fossa tumors.

Medulloblastoma

TREATMENT

Resection

Adjuvant therapy

Children ≥ 3 years: chemotherapy and craniospinal radiotherapy

Children < 3 years: chemotherapy

CASE 3

A **14 months** old male child, product of nonconsanguineous marriage, brought by his mother with presenting complaints of **abdominal swelling for 25 days and poor feeding for 10 days**. The child was previously doing well. On examination the child was afebrile, with weight 10 kg (50th-75th centile)and height was 76 cm (50th-75th centile). Bowel and bladder functions were normal. Child attained milestones as per the age. Immunized as per national immunization schedule. There is no food and drug allergies. On abdominal examination**, liver was palpable 8 cms below the right costal margin in mid clavicular line** and spleen was not palpable. Other systems were normal. CBC showed thrombocytosis(, Hb% was 11 gm/dl, WBC was 10,000/mm3 and RBC was 5.5 millions/mm3 of blood. Had **normal liver function tests .**

What is the next step in evaluation ?

EVALUATION

Abdominal US showed **echogenic solid mass** in the **right lobe** of the liver , with well defined capsule .The dimension being 65×87 mms. Further investigations in the form of CT scan confirmed the extent of the mass.

Serum AFP level was >1000 ng/ml. Hepatitis B and C and HIV tests were negative. **Liver biopsy** was performed under ultrasound guidance. The report showed cells arranged in solid sheets and trabecular pattern. The cells had distinct cell membrane and uniform nuclei with minimal pleomorphism and there was presence of fetal pattern and foci showing rosset formation. The mass from the right lobe of the liver was excised. No chemotherapy or radiotherapy was given as the tumor is localized and well circumscribed and also resectable with no metastasis.

AGE:	GENDER:	Chief Complaint
14 months	MALE	abdominal swelling and poor feeding

Figure 1: Child with abdominal lump and umbilicus was everted.

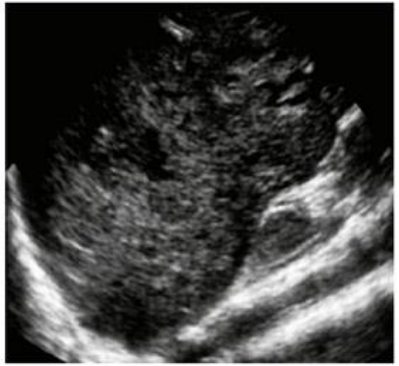


Figure 2: USG Abdomen showing echogenic soft tissue mass, well defined margin. Intralesional calcifications- are visible as areas of shadowing.

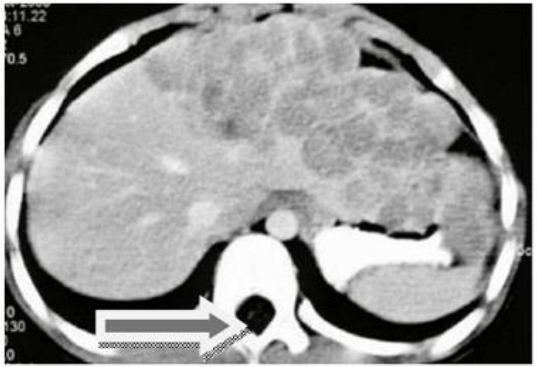


Figure 3: CT-Scan image showing heterogenousmass, and calcifications in the right lobe and left lobe of the liver. The mass is Hypoattenuated compared to surrounding liver. Necrotic and hemorrhagic areas were not seen.

Hepatoblastoma

EPIDEMIOLOGY AND RISK FACTORS

Hepatoblastoma is a rare tumor overall, but it is the **most common primary malignant hepatic neoplasm in children**, comprising two-thirds of primary liver tumors in this population. Ninety percent of the cases occur in children less than five years old, primarily before the age of two

For yet undetermined reasons, an increased incidence of hepatoblastoma is seen in children born **prematurely**.

In children and young adults, hepatoblastoma is almost **never associated with chronic liver disease**. Most cases are sporadic. However, in children, there are some inherited syndromes with an increased incidence of hepatoblastoma, which include **Beckwith-Wiedemann syndrome, trisomy 18, trisomy 21**

CLINICAL PRESENTATION

In children, hepatoblastoma has **no specific presentation** and often occurs as an asymptomatic mass in the liver but may occur with nonspecific symptoms such as abdominal pain, nausea, or vomiting; for unclear reasons, they are more often located in the right lobe. It classically arises within a healthy liver, unaffected by underlying disease.

Hepatoblastoma

DIAGNOSIS AND INTIAL EVALUATION

The majority of hepatoblastomas are first identified by imaging, but **Liver biopsy remains the gold standard diagnostic tool for confirming Hepatoblastoma.**

Radiologic evaluation plays a crucial role in optimizing treatment for hepatoblastoma. High-quality cross-sectional imaging is necessary for **accurate staging and treatment planning**. Ultrasound is particularly useful for infants with hepatoblastoma and can often detect a solid intrahepatic mass, predominantly in the right lobe. However, to assess vascular involvement more accurately, contrast-enhanced CT or MRI are recommended.

Laboratory evaluation in hepatoblastoma often reveals nonspecific findings. Liver function tests are typically normal or only mildly elevated. **Anemia and thrombocytosis are common**.

Alpha-fetoprotein (AFP) is the primary tumor marker for hepatoblastoma. In most patients, AFP levels are elevated. However, AFP is relatively **nonspecific** and cannot fully differentiate hepatoblastoma from conventional hepatocellular carcinoma (HCC). When AFP is elevated, considering the **patient's age** (younger ages favoring hepatoblastoma) and the presence of **underlying liver disease** (favoring HCC) can be helpful in suggesting the diagnosis.

Hepatoblastoma

DIFFRENTIAL DIAGNOSIS AND TREATMENT

Distinguishing hepatoblastoma from other similar tumors can be challenging, even with microscopic examination of tumor tissue. It is crucial to collaborate closely with pathologists to consider various entities in the differential diagnosis. These include **HCC, rhabdoid tumor of the liver, undifferentiated embryonal sarcoma of the liver, ossifying stromal-epithelial tumor, transitional liver cell tumors**.

The differentiation between hepatoblastoma and HCC can be particularly difficult due to overlapping histopathologic and gross features. When the biopsy specimen is small and contains only fetal-type cells, it becomes challenging to differentiate from well-differentiated HCC. Factors that may aid in differentiation include the patient's age, the presence of underlying liver disease (common in HCC, such as cirrhosis), extramedullary hematopoiesis in hepatoblastoma, and the likelihood of normal surrounding liver tissue in hepatoblastoma.

Treatment

- Complete resection of tumor.
- Cisplatin and doxorubicin adjuvant chemotherapy.
- More than 90% survival with multimodal treatment (surgery with chemotherapy).

OVERVIEW

Definition

- Rare in children.
- Fewer than 65% of malignant tumors are hepatoblastomas.
- Associated with Beckwith-Wiedemann syndrome.
- Usually arises from the right lobe of the liver and is unifocal.
- Two histologic types—epithelial and mixed.

Signs and Symptoms

- Generally present in first 18 months of life.
- Large, asymptomatic abdominal mass.
- Abdominal distention and ↑ liver size.
- Weight loss, anorexia, vomiting, and abdominal pain (as disease progresses).
- May spread to regional lymph nodes.

Diagnosis

- α-Fetoprotein (AFP) level helpful as marker.
- Diagnostic imaging includes ultrasound to detect mass, CT, or magnetic resonance imaging (MRI).

Differential Diagnosis

1. HCC
2. rhabdoid tumor
3. embryonal sarcoma
4. ossifying stromal-epithelial tumor
5. transitional liver cell tumors

Treatment

- Complete resection of tumor.
- Cisplatin and doxorubicin adjuvant chemotherapy.
- More than 90% survival with multimodal treatment (surgery with chemotherapy).

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Cancer Chemotherapy

By Omar Abu-Summaqa

Concise history and general principles of cancer pharmacotherapy.

- Chemotherapy is a term used originally to denote the use of drugs to treat infectious diseases.
- However, as some forms of cancer were hard to treat in the early and mid 20th century due to wide metastases, there was a huge effort in creating a drug that can target cancerous cells, now called: Cancer Chemotherapy. The first chemotherapy that was invented belong to a family called nitrogen mustard with its famous example, Cyclophosphamide.
- Traditionally, they affected the neoplastic cells (along with other cells, why?) by disturbing DNA, RNA or protein synthesis.
- Like microscopic organisms, cancerous cells have the ability to develop resistance to chemotherapy, hence, multiple chemotherapeutic agents are usually used to decrease and prevent resistance. (example?)

- Drug-Drug interactions are expected. It is important to know each agent inducers and inhibitors to maintain the chemotherapeutic levels wanted, otherwise, inducers and inhibitors will affect the enzymes (e.g. p450)
- Since they also affect normal cells, they can have numerous side effects. Side effects are either short term(most significant on S phase of the cell cycle) or long term. Since most chemotherapeutic agents have narrow therapeutic index, it is magnificent to recognize adverse effects early to adjust the dosing for each patient (why ?).
- Like other drugs, chemotherapeutic agents can be administered IM,IV and oral, usually IV route is used (why??)
- How to circumvent the BBB when administering chemotherapy ?

- Adjuvant vs neoadjuvant chemotherapy ?
- Which is better ?
- Why chemotherapy is used in almost all pediatric cancer ?

General short term side effects that any cancer chemotherapeutic can cause include:

- Nausea.
- Vomiting.
- Diarrhea.
- Alopecia.
- Infertility.
- Myelosuppression.
- Infusion reactions.
- Immunosuppression.
- Hepato and nephron toxicity.

Late term side effects of cancer chemotherapy in pediatrics

- Pituitary gland: 1) growth 2) endocrine
- Thyroid.
- Puberty and height.
- Cardiopulmonary.
- Renal.
- Second malignancies.
- CNS

Some of the most commonly used chemotherapeutics in pediatrics.

1. Cyclophosphamide: (alkylating agent)
   - MOA :Alkylates guanine; inhibits DNA synthesis.
   - Uses: ALL, lymphoma, sarcoma, brain Tumors.
   - Notable acute toxicity : Myelosuppression; hemorrhagic cystitis.

2. 6-Mercaptopurine : (anti metabolite)
   - MOA: Purine analogue.
   - Used mainly for ALL .
   - Notable acute toxicity: Myelosuppression; hepatitis; mucositis;

   NOTE** Allopurinol increases toxicity.

3. Doxorubicin and daunorubicin : (anthracyclines)
   - MOA: Intercalation, DNA strand breaks
   - Uses: ALL, AML, osteosarcoma, Ewing sarcoma, lymphoma, neuroblastoma
   - Notable acute toxicity: Cardiomyopathy, red urine, tissue necrosis on extravasation, myelosuppression, conjunctivitis, radiation dermatitis, arrhythmia.

4. Methotrexate (MTX): (anti metabolite)

- MOA: Folic acid antagonist;

inhibits dihydrofolate Reductase.

- Uses: ALL, lymphoma, medulloblastoma and Osteosarcoma.
- Notable acute toxicity: Myelosuppression (nadir 7–10 days), mucositis, dermatitis, hepatitis, renal and CNS effects with high-dose administration;

** note :prevent with hydration and leucovorin,
monitor levels.

5. Cytosine arabinoside (Ara-C). (anti metabolite)

- MOA: Pyrimidine analog; inhibits DNA polymerase.
- Uses: ALL, AML, lymphoma.
- Notable acute toxicity: Myelosuppression, conjunctivitis, mucositis and neurotoxicity.

6. Vincristine

- MOA: Inhibits microtubule formation.
- Uses: ALL, lymphoma, Wilms tumor, Hodgkin disease, Ewing sarcoma, neuroblastoma,
- Notable acute toxicity: rhabdomyosarcoma, brain tumors Local cellulitis, peripheral neuropathy, constipation, ileus, jaw pain, inappropriate ADH secretion, seizures, ptosis, minimal myelosuppression.

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