Solid tumors

Summary prepared by: Amr Qudeimat

This can be a tough topic to handle at this level as there are many different tumor histologies and locations that can be overlapping. Much of the details are of interest mainly to oncologists but it's vital that pediatricians are familiar with the general presentation of solid masses and how to start a working them up as this is usually precedes the referral to the oncologist. In addition to this, some level of detail may be helpful when it comes to the most common pediatric tumors.

Tumors are initially asymptomatic. Once they grow up to a critical mass, symptoms develop and are either due to the mass mechanical effect (which depends on both mass size and location), mediators produced by the mass (as in VIP secreting tumors and pheochromocytoma) or loss of function (e.g. Hypoglycemia in end stage liver tumors) . Examples of mechanical effects include: Pain, usually due to impingement on nerves or compromise of vascular supply, constipation or bowel obstruction, abdominal distention, headache due to increased ICP caused by a brain tumor, Horner's syndrome, paralysis, etc.

Since many of these symptoms are nonspecific as pain or constipation, timely diagnosis will rely heavily on a high index of suspicion coupled with recognition of atypical features of common nonspecific symptoms. Examples of this include prolonged worsening constipation not responding to liberal laxative use, anemia in a post pubertal male who consumes a healthy diet and has no obvious sources of bleeding or daily headache in a 5-year-old child.

We start with the symptoms to localize the problem; a patient with sudden onset lower limb paralysis and acute low back pain probably has a mass compressing the spinal cord. Imaging is commonly utilized in diagnosing almost all solid tumors. Generally, we start with simpler imaging modalities before proceeding with more time-consuming ones and those with high radiation exposure while keeping the patient's clinical status and needs in mind. For example, while an CT scan is the modality of choice for delineating most abdominal masses, starting with simple abdominal X ray films can be both faster and help recognizing obstruction or free air in the abdomen early on. Another example is that MRI is superior to CT scan for imaging brain tumors and involves no radiation. However, a CT scan is more appropriate in patients presenting with sudden severe headache and loss of coordination as it helps quickly rule out intracranial bleeds and increased intracranial pressure compared to the much more time-consuming MRI. Once the most life threatening and pressing conditions are dealt with, an MRI can be performed when the patient is more stable. All patients need complete blood counts and chemistries at baseline with further testing guided by initial suspicion and imaging findings. Below, is a short account of the most common and most significant solid tumors.

A) Brain tumors: although this is a very diverse group of many different tumors, they are collectively the most common solid tumor in children. They are the second most common malignancy of childhood after leukemias. They can be either primary brain tumors or metastatic tumors. Common presenting symptoms and signs can be nausea, vomiting, headache, behavioral and sleep cycle changes, weight changes, developmental delay, papilledema, bulging fontanels, cranial neuropathies, seizures, imbalance and loss of coordination/ ataxia. Early preference of one hand before the age of 2 years or change of handedness can be an alarming sign too. This means that an accurate illness history and a complete physical examination including a good neurologic exam is extremely important.

   Most brain tumors of childhood are infratentorial in location and the most common tumor is medulloblastoma which is a tumor of an embryonal origin. Most medulloblastoma cases are diagnosed under the age of 10 years. The main presenting symptoms are ataxia in addition to signs of increased intracranial pressure. Treatment relies on a combination of surgical excision where the more complete the excision the better the outcome is, radiation and chemotherapy. Overall cure rates are very good but long-term growth and neurodevelopmental delays in addition to endocrinopathies are common complications of radiation therapy.

A rare but grim brain tumor is diffuse intrinsic pontine glioma. The difficulty dealing with this tumor comes from the fact that its location within the brain stem and poor response to chemotherapy makes it uniformly fatal. Diagnoses relies on radiologic features as biopsies are generally too risky to obtain. Long term survivors probably were misdiagnosed to start with. Radiation therapy can be used for palliation.

Pilocytic astrocytoma are common brain tumors that can occur almost anywhere in the CNS. They are considered as low-grade tumors with a low metastatic potential. Gross total resection, if feasible, is generally curative.

Glioblastoma multiforme is a high-grade glioma with a very poor prognosis even with combined resection, radiation and chemotherapy.

Other brain tumor that won't be discussed in detail here include: pineoblastoma, ependymoma, spinal cord tumors and germ cell tumors.

B) Neuroblastoma: it's the third most common childhood malignancy and second most common solid tumor in children. Its an embryonal malignancy originating from the neural crest tissue of the sympathetic nervous system. The tumor can arise anywhere along the sympathetic chain, but the classical presentation is an abdominal suprarenal mass. Clinical presentation depends on the location of the tumor (neck mass, intrathoracic mass or abdominal mass) and metastasis (skin lesions, anemia due to bone marrow replacement, bony masses and bone pain, proptosis and raccoon eyes). It may present with Horner's syndrome if the stellate ganglion is involved. Paraneoplastic effects are a known association with neuroblastoma, examples are VIP secreting tumors and opsoclonus myoclonus syndrome were patients present with random eye movements, myoclonus and ataxia. This usually predicts a good prognosis although it may be associated with long term neurologic complications. Poor prognostic features include normal diploid DNA content in tumor cells, advanced stage disease, age above 18 months at presentation, higher risk histologic features (poorly differentiated tumors), and MYCN oncogene amplification. An exception would be stage 4S in infants (S for skin metastasis) where prognosis is excellent. Diagnostic evaluation includes: a chest/ abdomen/ pelvis CT scan, MIBG scan, bone marrow biopsy, spine MRI if involvement of the spine is suspected, urine/ serum testing for catecholamine metabolites (HVA and VMA) in addition to baseline blood counts and chemistries. Historically, overall neuroblastoma prognosis was very poor with surgery, chemotherapy and radiation (for select cases). Significant improvement in outcome was achieved in the past few decades with the addition of autologous stem cell transplant and antibody therapy.

C) Wilms tumor(nephroblastoma): it's the most common pediatric renal malignancy. Renal cell carcinoma is another, less common tumor and won't be discussed in detail here. Most cases of Wilms tumor are unilateral although up to 10% can be bilateral. It can be associated with some malformations in up to 10% of the cases. This includes: aniridia, hemi-hypertrophy, Genito-urinary malformations and others. Having one of the malformations associated with Wilms tumor can lead in many cases to earlier diagnosis of the disease. Patients with over growth syndromes including up to 10% of children with Beckwith- Wiedemann syndrome and some children with Perlman syndrome develop Wilms tumor. About 5% of patients with isolated hemi-hypertrophy also develop Wilms tumor. Also, some non-over growth syndromes are associated with Wilms tumor such as WAGR syndrome (Wilms, Aniridia, GU malformations and mental retardation), bloom syndrome and Denys-Drash syndrome (nephropathy, male pseudo hermaphroditism and Wilms tumor). Of interest, about 2% of all Wilms tumor cases can be familial. Many genes play a role in the development of Wilms tumor including WT1(Wilms tumor 1) WT2 and WTX genes. Most Wilms tumor patients have favorable histology with excellent prognosis. About 8% have anaplastic histology. The most common presentation is an asymptomatic abdominal mass. Occasionally, abdominal pain, hypertension, anemia and hematuria may be present. Evaluation includes careful history and examination to document blood pressure and check for potential congenital anomalies the presence of which may warrant evaluation by a geneticist, blood counts, UA, blood electrolytes, liver function testing and chest/ abdominal/ pelvic CT scan or MRI. While lower stage disease may be managed with surgical excision alone, higher stage disease require chemotherapy the possibility of radiation for situations like lung metastasis.

D) Osteosarcoma: it's a rare childhood tumor. It can occur either denovo or as a long-term (around 10 years post exposure) side effect to radiation therapy. Patients with hereditary retinoblastoma are also at high risk for developing osteosarcoma. It can also be part of Li-Fraumeni syndrome (Tp53 mutation). The classical clinical presentation is pain and a mass at the site of the primary tumor. This tumor typically involves the metaphysis of long bones. Most common sites are the distal femur followed by the proximal tibia followed by proximal humerus. The tumor can spread in skip lesions pattern or through hematogenous spread to the lung and other bone locations. Diagnostic work up includes plain X ray films that tend to show osteoblastic, osteolytic or a mixture of these 2 lesion types. Classical X ray findings include a Codman triangle caused by elevation of the periosteum and a sunburst pattern due to extension of the tumor through the periosteum. In addition to X rays, a chest CT scan is done to rule out pulmonary metastasis in addition to a biopsy. Treatment relies on surgery and chemotherapy administration. Radiation is not part of treating osteosarcoma.

E) Ewing sarcoma: is another type of bone tumor. It's a primitive neuroectodermal tumor. As in osteosarcoma, it presents with pain at the primary tumor site but, unlike osteosarcoma, Ewing sarcoma tends to affect the axial skeleton more often. Most common involved location is the pelvis. Other common locations include the femur and ribs. It can present with systemic symptoms as fever and weight loss. Metastasis can affect the lungs, bone and bone marrow. Work up is similar to osteosarcoma but in addition includes bilateral bone marrow biopsies given the potential to metastasize to the marrow. The classical plain X ray finding described is the onion skin appearance, but Codman triangles and sunburst patterns can be seen too. Treatment relies on surgery, chemotherapy and radiation. Autologous stem cell transplant may be considered for select cases.

F) Retinoblastoma: is a rare childhood tumor affecting the retina. The vast majority of cases present by the age of 5 years. It has 2 major forms. The hereditary form affects about 25% of patients, usually bilateral and multifocal and is due to germline mutations in the RB1 gene which is a tumor suppressor gene. The median age of presentation is around 15 months. On the other hand, the non-hereditary form forming the majority of cases is unilateral or unifocal and is due to mutations in RB1 gene in somatic cells. Median age of presentation is about 30 months. The most common presenting feature is leukocoria, but strabismus, nystagmus, glaucoma, periorbital cellulitis, proptosis and buphthalmos, can be other features. Diagnosis depends on examination under anesthesia of the retina for direct visualization of the tumors and evaluation of intraocular pressure in addition to ocular ultrasound, orbit and brain MRI, bone scan and bone marrow studies (evaluate for metastasis). The most common metastatic sites are the bone, bone marrow, liver and CNS. Genetic counseling is a vital corner of the workup and management of this disorder. Treatment of retinoblastoma requires the provision of multidisciplinary care aspects and depends on laterality and potential vision outcome / eye salvage chances. Surgical excision, chemotherapy, radiation and laser photocoagulation are all used modalities for this type of tumor. Retinoblastoma survivors are at high risk for developing second cancers post therapy. Most of these second cancers, but not all of them are radiation induced. The most common second cancer is these patients is osteosarcoma followed by soft tissue sarcomas, melanoma/ other skin cancers, lung cancer and others. A peculiar clinical entity that is worth mentioning here is trilateral retinoblastoma which is the presence of a midline pineoblastoma in a patient with bilateral retinoblastoma. This condition is characterized by a very poor outcome.

G) Hepatoblastoma: it's the most common liver malignancy in children and typically affects infants and young children with a median age at diagnosis of 19 months and the vast majority of patients are under the age of 15 years. Prematurity and low birth weight are risk factors for this tumor for unclear reasons. About 5% of hepatoblastoma patients also have familial adenomatous polyposis syndrome showing the importance of obtaining and accurate and complete family history in many of the patients with solid tumors. It typically presents with a painless abdominal mass (pain present in advanced disease), weight loss, loss of appetite and most cases have elevated alpha feto protein level. If metastasis occurs, its usually to the lungs but other locations are also possible as the brain and peritoneum. Workup, in addition to biopsy includes CT scan imaging (or MRI), abdominal ultrasound and AFP levels. While normal AFP levels can't rule out hepatoblastoma they are associated with a

poorer prognosis and elevated levels can be followed to assess response to treatment. Treatment is based on a combination of surgical resection and chemotherapy. Those with unresectable tumors may need a liver transplant to achieve cure.