PEDIATRIC SURGERY *Update
Volume 61 No. 05 NOVEMBER 2023

Neuroendocrine Gastrointestinal Tumors

Neuroendocrine tumors (NET) are rare, slow-growing epithelial tumors originating from cells within the neuroendocrine system and affecting 1-3 per 100,000 children per year. African American has the highest reported incidence. Neuroendocrine tumors can arise in the lung, bronchial tree, thymus, testis, thyroid, and gastrointestinal tract. The most common system affected by these tumors is the gastrointestinal tract. NET represent the most common gastrointestinal malignancy in children. NET were originally named carcinoids, in reference to the carcinoma-like characteristic microscopic features in a tumor with benign behavior. This term is now use solely in the context of carcinoid syndrome. NET can either be sporadic (most commonly) or occur in the context of familial syndromes such as multiple endocrine neoplasia, Von Hippel Lindau and neurofibromatosis. Pathologically, NET are small blue cell tumors with specific neuroendocrine markers for enolase, synaptophysin and chromogranin. Midgut NET are argentaffin positive, while hindgut NET is argentaffin negative staining. As an Apudoma, they contain neurosecretory granules filled with serotonin, histamine, corticotropin, dopamine, and kallikrein. Origin of NET in the bowel and pancreas is from pluripotent progenitor cells. NET are classified on degree of differentiation, proliferative index Ki-67, and its mitotic count, while staging uses the TNM system. 12% of NET present with distant metastasis at initial presentation. NET are classify clinically as functional or non-functional depending on signs and symptoms specific to the substance they produce such as pancreatic insulinomas or serotonin in cases of functioning NET of the midgut (carcinoid syndrome). Carcinoid syndrome associated with midgut NET occurs when the disease has metastasize to the liver. Non-functional NET are usually asymptomatic and found incidentally (appendix), or symptomatic due to local pressure effect. Pancreatic NET comprise 33% of all NET in the GI tract, are frequently multifocal and most (60%) are non-functional, large size and late presentation with 50% metastasizing liver at clinical presentation. For functioning pancreatic NET diarrhea (gastrinomas) and diabetes (glucagonoma) are the two most common presenting features. Insulinoma is the most common pancreatic functioning NET. Others are Vipomas and somatostatinoma. The appendix is the most common site (80%) for gastrointestinal NET in children with a 16% malignant rate and they are found incidentally after emergency or interval appendectomy (0.08%). Two-third of appendix NET are located in the tip of the appendix. Tumor size is highly predictive of outcome. Mean age of presentation is 14 years with female gender predilection. 86% are incidentally identified after appendectomy. Mean size of appendiceal NET is 0.6 cm, with 44% demonstrating serosal extension and 15%

lymphovascular invasion. Infiltration through the appendiceal wall layers into periappendiceal fat or mesoappendix is reported in 60% of cases. Mitotic index or proliferative index of appendiceal NET does not correlate with overall survival. Small bowel NET affect the ileum most commonly, and most patients present with local lymphatic spread and distant metastasis. Gastric NET are very rare in children. Colonic and rectal NET are also extremely rare in children, present with carcinoid syndrome, contain glucagon, and 50% are found incidentally during colonoscopy. Diagnosis of NET is confirmed by histopathology, while secreting functioning NET will determine the hormone involved. Localizing imaging studies include contrast enhanced CT, MRI, somatostatin receptor scintigraphy (Octreotide scan), along with Gallium-68 PET-CT for assessing metastatic tumors. Gallium-68 PET/CT has low toxicity, low radiation exposure, fast administration and clearance time making it the most reliable diagnostic modality for children. Patients with metastatic NET have a significant higher level of chromogranin A than those with localized disease. Higher serum levels of pancreastatin are also associated with poor prognosis and is able to distinguish patients at high risk of recurrence. In the absence of persistent carcinoid syndrome, postoperative scans and serum biomarkers are unhelpful. NET should be managed with complete surgical resection whenever possible. With non-resectable or metastatic disease, surgery should aim to ablate or debulk the tumor to significantly improve length of survival and quality of life. In cases of appendix NET a right hemicolectomy is indicated for tumors larger than 2 cm, goblet cell tumors regardless of size, and poorly differentiated tumors. Well differentiated tumors less than 2 cm that breached the serosal surface or invade the mesoappendix by more than 3 mm, are located in the base of the appendix or demonstrate mesenteric lymph node involvement could also benefit from hemicolectomy, though this is controversial in children. Complete resection of a well-differentiated NET < 2 cm does not require a right hemicolectomy. It is believed that due to the benign indolent nature of appendiceal NET, hemicolectomy may be too aggressive for pediatric patients. The consensus is that appendectomy alone is sufficient for NET of the appendix regardless of tumor size or local invasion with an excellent prognosis. Appendiceal NET in children show benign behavior and a particularly low propensity to regional node diffusion and metastatic spread even when they are larger than 1 to 2 cm, or present vascular invasion or extension to mesoappendiceal fat. Chemotherapy (streptozotocin, 5-FU, doxorubicin) is reserved for highly proliferative NET tumors with large burden. Prognosis of appendix, colon and rectum NET is better than other sites. Overall, five-year survival of NET in children is 78%. Nonsurgical treatment options include somatostatin analogues, molecularly targeted therapy, cytotoxin therapies, and peptide receptor radionuclide therapy.

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Lung Hernia

Lung hernia is defined as a protrusion of lung tissue through one of its bounder structures. Lung herniation is a rare condition that can be classified on the basis of anatomic location and etiology. In the majority of patients, the lung tissue herniates through the intercostal space as result of trauma or after open or laparoscopic thoracotomy procedures. Lung hernias can be congenital (20%) or most commonly acquired (80%). Congenital lung hernias are caused by attenuation of the endothoracic fascia occurring at the thoracic inlet or the intercostal space. They also are associated with costal or cartilage malformations such as rib or intercostal hypoplasia. They occur either at the thoracic inlet or at the intercostal spaces whereas weakness of the fascia is usually combined with absence of the intercostal muscles. Most congenital lung hernias present in childhood, but they may be asymptomatic and present later in life. Acquired lung hernias usually results from trauma to the chest (penetrating or blunt), from preceding procedures with inadequate closure of the chest wall, spontaneous, or after local pathological conditions such as a tumor, abscess in the chest wall or tuberculosis. Trauma (penetrating or blunt) accounts for the majority of acquired lung hernias, or from preceding operative procedures with inadequate closure of the herniated lung. Postoperative intercostal lung hernias are reported more commonly after less extensive surgical procedures such as video-assisted thoracoscopy, than after major thoracic interventions. This is due to a less meticulous closure of the smaller incisions. Post-thoracotomy lung hernias occurs most commonly on the right side in the fifth intercostal space containing lung tissue. Predisposing factors include hyperinflation caused by COPD, poor tissue quality and healing capacity resulting from diabetes, obesity, and oral steroid use. Spontaneous lung hernias usually develop as a consequence of a sudden increase of intrathoracic pressure such as during intense coughing, sneezing, musical instrument, or glass blowing or strenuous lifting. The eight to ninth ribs tend to be the most common location of herniation possible due to the lack of muscle support from the trapezius, latissimus dorsi, and rhomboid muscles to the posterior portion of the thorax. Pathologic hernias are the least common variety and usually represent sequelae of chest wall or breast pathology such as abscess or empyema necessitans, malignant tumors and tuberculous osteitis. By anatomy, lung hernia can be classified as apical (cervical), thoracic (intercostal), mediastinal, or diaphragmatic in location. A lung hernia usually presents as a soft, tender, visible and palpable subcutaneous mass that enlarges on physical strain, coughing or after a Valsalva maneuver. Early clinical diagnosis may be difficult since the symptoms of lung herniation appear to overlap those resulting from intercostal neuritis or neuralgia. Chest pain associated with lung herniation most likely results from parietal pleura irritation. Chronic intercostal neuralgia can develop either due to intercostal nerve injury of the associated rib fracture or due to chronic compression by herniated lung tissue. A visible or palpable bulging may be present (80%) as well as bruising of the surrounding area (60%). Diagnosis of a lung hernia is confirmed with a chest film or CT-Scan. Chest films

shows a subcutaneous hyperlucency containing pulmonary vessels corresponding to a localized collection of air. Requesting an optimal oblique view of the plain chest film eliciting a cough reflex may increase likehood of diagnosis. Chest CT images demonstrate the herniated lung, the hernia orifice in the chest wall, the hernia sac, as well as their anatomic relation within the pectoral and intercostal muscles. Management of lung hernias depends on symptoms, location, and size. Asymptomatic lung hernias in a supraclavicular (cervical) location usually does not require treatment since they remain unchanged and asymptomatic unless they impinge the T1 nerve area causing compression and cervical neuralgia. Herniation occurs through a defect in the Sibson's fascia and the apical segment of the lung protrudes in between the scalenus anterior and sternocleidomastoid muscle. Apical lung herniation can be spontaneous and has also been reported in wind instrument players, patients with chronic lung disease and weightlifters. The apex of the lung is usually retained within the thorax by the muscles of the thoracic inlet, Sibson fascia and the parietal pleura. Apical lung hernias are typically identified on plain chest films as apical radiolucent areas of variable size that extends into the neck. Surgical treatment is rarely needed unless the hernia causes symptoms or undergoes incarceration. This type of lung hernia can cause problems during insertion of internal jugular or subclavian catheters by resulting in inadvertent pneumothorax. Complications to an untreated lung herniation include pneumonia, pneumonitis, and pleural scarring. Treatment of symptomatic lung hernia is surgical and is determined by factors such as size and pain, incarceration or strangulation of lung tissue, and paradoxical respiration with poor ventilation. Repair is performed using surround tissues or synthetic material including polytetrafluoroethylene and/or propylene mesh. Surgery is often associated with a complete resolution of symptoms and low-associated morbidity.

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Esophageal Duplication Cysts

Esophageal duplication cysts are rare congenital anomalies of the alimentary tract in children. It is one of the causes of acute respiratory distress in infancy and children. Duplications of the bowel are found 50% in the midgut, 36% in the foregut and 12% in the hindgut. Esophageal duplication cysts accounts for 15-20% of all enteric duplication cysts. The most common location of enteric cysts is the ileum with the esophagus being the second most prevalent. Esophageal duplication cysts can occur in the proximal, middle, and lower third of the esophagus, and more than 90% do not communicate with the lumen.

Esophageal duplication cysts most commonly occur in the lower third of the esophagus. Ventral budding of the lung primordia from the foregut occurs at the 3-4 weeks of gestation, with aberrations in this process during this stage may result in duplications of the esophagus or bronchi. When foregut cysts are associated with vertebral anomalies, they are called neuroenteric cysts. Neuroenteric cysts can have some communication with the spine. Pathologically an esophageal duplication cyst is attached to the esophageal wall, is covered by two muscle layers sharing a common wall, and the lining can be squamous, columnar, cuboid, pseudostratified or ciliated epithelium. Esophageal duplication cysts may contain ectopic gastric mucosa and pancreatic components. Presenting symptoms may include those of either respiratory or intestinal origin including compression of the esophagus or trachea due to mass effect, pain, infection, bleeding, or perforation. These include dysphagia, epigastric discomfort, and retrosternal pain. In many series enteric cysts are asymptomatic and discovered incidentally on imaging or at the time of surgery for other indications. For children with symptoms CT, MRI, and endoscopic ultrasound (cardiac point-of-care ultrasound) offer excellent soft tissue contrast and the capabilities of multiplanar imaging to identify and evaluate the cyst. Imaging delineates the size, location, extent, and anatomic relationship of the cyst with surrounding structures. The diagnosis of an esophageal duplication cysts can be suspected antenatally by ultrasound as a smooth, spherical, or tubular structure with well-defined walls. The differential diagnosis include bronchogenic cysts and neuroenteric cysts. Complete excision is the treatment of choice for both symptomatic and asymptomatic incidentally discovered esophageal duplication cysts because of the high risk of obstructive respiratory problems and because these cysts do not regress spontaneously and occupy space causing symptoms ultimately. Malignant transformation, though rare has been described in children and adults. Incomplete excision, needle aspiration, and marsupialization have an unacceptable high rate of recurrence. To achieve complete resection a defect in the muscular layer of the esophageal wall is needed due to their integral relationship. The defect in the esophageal wall can create a pseudodiverticulum, reason why most surgeons advocate suture closure of the muscular defect or buttressing the defect with a 360-degree fundoplication to regain the antireflux function of the esophagogastric junction. The more serious complications such as cyst recurrence, diverticulum, stricture, and chylothorax occurred in patients whose muscle layer was left opened. Laparoscopic excision is a safe and effective approach to lesions in the distal esophagus. Thoracoscopic resection is utilized for esophageal duplication cysts found in the upper or middle third of the esophagus.

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**** PSU 1993-2023***
ISSN 1089-7739