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Pediatric pulmonary tumors: primary and metastatic

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Review

Pediatric pulmonary tumors are rare. There is often a significant delay in diagnosis of pulmonary tumors secondary to their rarity and nonspecific presenting physiologic and radiographic findings. A high index of suspicion in pediatric patients with recurrent or persistent pulmonary symptoms is of paramount importance in diagnosing pulmonary tumors at an early stage. Malignant pulmonary tumors are more frequently diagnosed than benign lesions, with metastatic cancers being the most common. Complete surgical resection remains the basis of therapy for primary lesions, and its role in secondary cancers is becoming more established. Adjuvant therapies are frequently employed depending on the precise tumor involved. Mortality rates vary greatly depending on tumor location, stage, and type.

Primary pediatric lung neoplasms are rare entities. Secondary cancers far outnumber primary tumors, and one report documents that 80% of all lung tumors, and over 95% of all malignant lung tumors, are metastatic disease from nonpulmonary cancers.[1] However, the number of neoplastic lesions pale in comparison to benign pulmonary disease processes. Reports have documented a ratio of 1:5:60 for primary cancers to metastatic lesions to benign disease entities in the pediatric lung.[2,3] Secondary lesions encompass diseases from most known pediatric cancers, including the adrenal gland, thyroid gland, gonads, liver, kidney, soft tissue, and bones.

Two comprehensive series to date (published a decade apart with the second building on the first)[4,5] have attempted to document the quantitative and qualitative aspects of these lesions by combing through institutional series and combining these cases with others reported in the medical literature resulting in data comprising over 383 patients. These series document that the majority of primary lung tumors are malignant (65-76%) with an overall mortality rate of 30%. However, benign pulmonary masses are not without significant mortality (8%) owing to the anatomic location of many of these lesions and their propensity to invade into surrounding structures in the mediastinum. Anatomically, primary lesions arise from both the tracheobronchial tree and pulmonary parenchyma proper, and they include a wide variety of histological subtypes: benign (inflammatory myofibroblastic tumors, 52%; hamartomas, 23%) and malignant (bronchial adenoma, 40.5%; bronchogenic carcinoma, 16%; pleuropulmonary blastoma, 15%).

Presenting symptoms can vary widely depending on the tumor type, size, rate of proliferation, malignant potential, vascularity, and the location of the tumor within the respiratory system. Symptoms for benign and malignant disease processes differed.[4,5] Benign lesions were asymptomatic in the majority of cases (24%) owing to the fact that they are more often peripheral lesions. The most common symptoms for benign lesions, when present at diagnosis, were fever (14%), cough (12%), and pneumonitis (10.5%). For primary malignant lesions, however, cough (35%), pneumonitis (23%), fever (18%), respiratory distress (12%), and hemoptysis (11%) were the most common findings, and this correlates with the fact that the most common tumors, bronchial adenomas, are predominantly endobronchial lesions. Only 6% of patients with malignant lesions were asymptomatic. There is often a delay in diagnosis of these lesions in children due to the nonspecific nature of many of the

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symptoms and their extreme rarity.[1,6-9] Often, infectious causes or reactive airway disease are the presumed diagnoses, and the patients are treated medically for several months or even years before diagnosis.[1,5,7]

Diagnostic studies initially consist of chest radiographs. Findings on these studies are helpful but are not specific for any single entity, and include atelectasis, hyperinflation, infiltrative processes, mass lesions, pleural or pericardial effusions, and hyperlucency. Many of these findings, as previously mentioned, will be attributed to more common diagnoses, such as reactive airway disease, foreign body aspiration, or infectious processes. Obviously, a mass found on a chest radiograph will prompt further imaging studies, but this is not often appreciated, especially for small, centrally located lesions. Furthermore, combining the symptoms of coughing and wheezing with hyperlucency on chest radiographic examination would likely be more suspicious for a foreign body inhalation than a pulmonary tumor based on the frequency of the two lesions. If suspicions and symptoms persist, computed tomography with three-dimensional reconstruction is the next modality employed. It is more sensitive (97%) than a chest radiograph in detecting masses, especially for central lesions.[10,11] The specificity of computed tomography, however, is low for pulmonary lesions, except for the pathognomonic "popcorn-like" calcifications of hamartomas[12] and the minority of carcinoid tumors that are calcified (26%).[13,14] Magnetic resonance imaging for pulmonary hamartomas[15] and carcinoid tumors[16,17] has been described, but it is not widely employed. Furthermore, carcinoid tumors can also be diagnosed by functional imaging techniques that rely on radiolabeled peptide analogues that react with specific somatostatin receptors found in increased number on carcinoid tumors with a high degree of sensitivity and specificity.[18,19] Although fluorodeoxyglucose (FDG) positron emission tomography has a high sensitivity and specificity in identifying increased metabolic activity, and hence malignancy in solitary pulmonary nodules,[20] carcinoid tumors are not avid.[21] Furthermore, neither magnetic resonance nor functional imaging studies have gained widespread applicability or acceptability in the pediatric population in the evaluation and management of pulmonary lesions.

Bronchoscopy, rigid or flexible, is useful in examining patients with persistent symptoms and/or radiographically defined lesions, especially if centrally located.[22,23] Although the possibility exists for macroscopic inspection, pathologic sampling, and therapeutic treatment of these lesions, only gross inspection is readily recommended in treating pediatric lesions. Bronchoscopic biopsy can be employed as well, but again only for endobronchial lesions, and the possibilities of indeterminate pathologic analysis from small sample size and poor sample quality as well as the risk of hemorrhage with fatal outcome from this approach are significant.[7,24,25] Therapeutic bronchoscopic resection and treatment using a combination of mechanical, thermal, radiation, and photobiologic therapies can be performed,[26,27] but only for endobronchial lesions. Furthermore, the extent of these tumors is notoriously underestimated on bronchoscopy, and hence, they are often referred to as the "tip of the iceberg" lesions. Finally, this mode of treatment has not been universally accepted by the pediatric medical community and is only recommended for small, benign lesions where complete excision is likely.[2,5]

Operative exploration with total gross and microscopic resection of all involved tissues is recommended for all types of lesions, regardless of histologic subtype.[2,4,5] Both open and minimally invasive techniques have been employed in the resection of these lesions; however, the larger and more centrally located lesions that may require complicated sleeve resections or tracheobronchial reconstruction are more suitable for a formal thoracotomy. The goal of any procedure, however, should be the preservation of as much normal parenchyma as possible. Caution must also be mentioned in regard to pneumonectomy in an infant or young child, for severe kyphoscoliosis may develop.[28] Therefore, parenchymal-sparing resections are recommended, if possible. A proposed treatment algorithm for the management of pediatric lung lesions is shown in Figure 1.

Benign lesions

Inflammatory myofibroblastic tumor (IMT)

IMT is a myofibroblastic spindle cell soft tissue tumor with infiltrative plasma cells, lymphocytes, and eosinophils as defined by the World Health Organization (WHO)[29] (Figure 2). It has been given many other names in the last half-century in the medical literature, the most well-recognized names being inflammatory pseudotumor and plasma cell granuloma. It was first described in 1939 as a primary pulmonary lesion,[30] and theory has held that it forms as a reaction to a previous tissue insult.[31] Various antecedent infections have been described in many reports with rates varying from 5% to 37%.[32-35] Furthermore, viral etiologies for these lesions have also been proposed after molecular constructs of the Epstein–Barr and Human Herpesvirus-8 viruses were recovered from these lesions,[36-40] but these theories are as yet unproven. Though traditionally considered benign, recent molecular analysis has cast doubt on this assumption. The WHO has defined this tumor as an intermediary lesion that has been characterized by a molecular rearrangement on chromosome locus 2p23 involving the tyrosine kinase receptor anaplastic lymphoma kinase (ALK) involved in other forms of malignancy.[41] Although this genetic lesion has been associated in some IMTs,[42-44] it has not been uniformly documented in all lesions, and debate continues on the true nature and malignant potential of this lesion.

It is the most common benign pediatric pulmonary lesion representing more than 50% of all documented benign lesions.[4,5] It is predominantly a peripheral lesion that has a tendency to grow slowly, but it can invade local structures