TUMORS, BENIGN

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Abstract
Benign tumors of the lung and pleura encompass a wide variety of epithelial and nonepithelial tumors that have an excellent prognosis in general. Many of these lesions are discovered incidentally in chest radiographs carried out for other reasons, most being asymptomatic at the time of presentation. Such benign tumors can occasionally produce symptoms related to bronchial obstruction (e.g., bronchial papillomas and mucous cell adenomas), or because of compression of lung parenchyma by sizable tumors (such as large solitary fibrous tumors of pleura/lung). Symptoms when present may include hemoptysis, cough or dyspnea, and other manifestations only rarely. Only exceptionally do benign lesions of the bronchus undergo malignant transformation (specifically the development of squamous cell carcinoma in tracheobronchial papillomatosis). In part, the importance of benign tumors of lung and pleura lies in the necessity to discriminate between them and malignant neoplasms of the respiratory tract.

Introduction
The borderland between inflammation/hyperplasia and benign neoplasia, and between benign versus malignant neoplasia, is poorly delineated or controversial for many disorders of the lungs and pleura. Accordingly, the selection of disorders discussed in this article is to some extent arbitrary (e.g., minute meningothelioid nodules have been included whereas carcinoid tumorlets have not, partly because the latter are considered to represent reactive hyperplasias of neuroendocrine cells).

The presenting clinical manifestations of benign tumors of the lung and pleura and their complications are largely dependent upon (i) the anatomical site where the lesions arise, and (ii) their size. Tumors arising within large airways can present with symptoms related to bronchial obstruction and/or hemoptysis, whereas those affecting the lung parenchyma or pleura are frequently discovered in radiographs taken for other reasons – unless they are large enough to produce compression of the lung with dyspnea, or attention is drawn to their existence by other factors, for example, the production of insulin-like growth factor (IGF) by some pleuropulmonary solitary fibrous tumors. Therefore, for the sake of convenience, the tumors discussed in this section are grouped according to whether they arise from large airways, lung parenchyma or the pleura, or a combination of different anatomical sites (e.g., pleural and intrapulmonary solitary fibrous tumor).

Benign Tumors of Large Airways

Solitary Squamous, Columnar, and Mixed Papillomas of Bronchus

Solitary bronchial squamous papillomas are rare lesions found mainly in middle-aged adults, and slightly more often in males than females. Solitary squamous papillomas of this type typically have histological appearances equivalent to papillomas found elsewhere, related to infection by human papilloma virus (HPV), and they can occur in association with HPV-related squamous papillomas of the larynx and upper aerodigestive tract. In small fiberoptic bronchial biopsies, discrimination between solitary squamous papilloma and well-differentiated squamous cell carcinoma can be problematic. Up to about 20% recur, and squamous cell carcinomas have been reported at the removal sites for these papillomas, suggesting that a few can transform into squamous carcinoma.

Columnar papillomas are extremely rare lesions that comprise arborizing to club-shaped fronds covered by columnar epithelium (Figures 1 and 2) and, as the term implies, mixed papillomas represent a hybrid of columnar cells and squamous elements.

Figure 1 Glandular papilloma of bronchus. The papilloma distends and occludes the bronchial lumen. The wall of the bronchus is depicted at right. Case contributed by Dr A S Pieterse, Adelaide, South Australia.
change, by surgical resection appropriate for conventional non-small cell carcinomas of lung.

**Multifocal Respiratory/Bronchial Papillomatosis**

In cases of multifocal bronchial papillomatosis, HPV infection is typically acquired during vaginal delivery from an HPV-affected mother. Papillomatosis develops during early life, and children so affected typically develop oropharyngeal and/or laryngotracheal papillomatosis, which may thence spread to affect more distal airways. In some cases, the papillomatosis can extend into lung parenchyma, resulting in cavitating lesions for which the distinction between cavitary papillomatosis versus supervening malignant change with the development of a cavitary squamous cell carcinoma can be exceedingly difficult or impossible on either radiological grounds or on small biopsy or fine-needle aspiration samples. Children affected by multifocal tracheobronchial papillomatosis typically develop a combination of symptoms that can include hemoptysis, manifestations of bronchial obstruction with wheezing, and/or recurrent pneumonia.

**Benign Tumors of Bronchial Glands: Mucous Cell Adenoma and Bronchial Analogs of Benign Salivary Gland Adenomas**

The expression ‘bronchial adenoma’ as a blanket term for indolent bronchial lesions has long outlived its usefulness; it was always beset with imprecision because it encompassed a group of indolent low-grade malignant neoplasms, including carcinoid tumors and adenoid cystic and low-grade mucoepidermoid carcinomas of bronchus. For bronchial lesions, the term ‘adenoma’ should be restricted nowadays to mucous cell adenoma of bronchus, papillary adenoma, and pleomorphic adenoma (mixed tumor), with nomenclature specific for each neoplasm.

Benign mucous gland adenoma (MGA), papillary adenoma, and pleomorphic adenoma of bronchus are extraordinarily rare neoplasms. For example, the textbook *Practical Pulmonary Pathology* published in 2005 refers to a study of over 3000 pulmonary tumors where there were no examples of MGA, and up to 1995, only 10 cases were found in the files of the Armed Forces Institute of Pathology in Washington, DC. MGAs can arise in any of the major or segmental bronchi and although some are asymptomatic, others can produce manifestations of bronchial obstruction. Characteristically, MGAs comprise microcystic collections of cuboidal to columnar mucus-producing glandular cells.

The main differential diagnosis for MGA is a low-grade mucoepidermoid carcinoma, characterized by an admixture of squamous or intermediate cells, whereas MGAs consist exclusively of microcystic mucus-producing glandular structures.

The very rare bronchial gland oncocytoma requires distinction from oncocytic carcinoid tumor and even metastatic tumors with oxyphilic cells.

**Benign Tumors of Nonepithelial Components of Bronchial Walls**

Benign Schwannian or perineurial tumors of bronchi (Schwannoma, neurofibroma) are rare, but may be encountered in particular among patients with type I von Recklinghausens neurofibromatosis. Otherwise, these lesions are most likely to represent incidental findings at bronchoscopy and are sometimes contained in biopsy samples.

Perhaps the most important benign neural tumor found in bronchi is the granular cell tumor (GCT, granular cell neurofibroma, Abrikossoff’s tumor). Again, some GCTs are asymptomatic and are found incidentally at bronchoscopy whereas others can be large enough to produce bronchial obstruction, cough, or hemoptysis. GCTs comprise uniform populations of rounded to fusiform cells with finely granular cytoplasm. Characteristically, these lesions have an immunophenotype of Schwannian differentiation, with positive labeling for S-100 proteins or myelin basic protein, and on electron microscopy they are characterized by myriad secondary lysosomes.

**Benign Tumors Affecting Lung Parenchyma and Bronchi**

**So-Called Localized Chondromatous Hamartoma**

Although the great majority of localized chondromatous hamartomas (LCHs) arise within the peripheral
lung parenchyma, the occurrence of these lesions in larger airways is well documented, where they can produce hemoptysis and/or signs and symptoms of bronchial obstruction.

Although the term ‘hamartoma’ implies a non-neoplastic developmental disorder, there appears to be a consensus that LCH represents a benign connective tissue tumor that typically shows chondroid differentiation along with myxoid fibrous tissue and adipose tissue, and which entraps the epithelium of small airways as it enlarges (Figure 3). For peripheral LCHs, calcification within the cartilaginous tissue may produce a popcorn appearance that allows confident radiologic diagnosis. These lesions tend to shell out from the lung parenchyma quite easily at surgery. Although pediatric cases have been recorded, most LCHs are found in adults between the ages of about 40 and 60 years, and in some cases they can be seen to enlarge in serial chest radiographs.

Most LCHs represent solitary lesions but they can be encountered as part of the lesional triad that includes pulmonary hamartoma, extra-adrenal paragangliomas, and gastric epithelioid stromal tumors (Carney’s triad).

Benign tumors of smooth muscle in the lung are extremely rare. Lymphangioleiomyomatosis (LAM) has been excluded from this article, and although some authorities include benign metastasizing leiomyoma among the benign connective tissue tumors of bronchus/lung, these lesions are generally considered to represent indolent pulmonary metastases/emboli from a low-grade uterine leiomyosarcoma that lacks cytological markers of malignancy.

Lipoma of bronchus (Figure 4) is an extremely uncommon lesion, and requires distinction from a localized hamartoma that shows a predominance of adipocytic differentiation. Lipomas are similarly rare within the peripheral lung tissue.

Glomus cell tumors and glomangiomyomas of bronchus/lung are even rarer, as are true hemangiomas of bronchus and lung.

Mature (Differentiated) Teratoma

Primary intrapulmonary mature teratomas (dermoid cysts) are extremely rare tumors (Figure 5). These lesions must be distinguished on clinical grounds from metastatic germ-cell tumors with teratomatous elements, where the malignant components such as embryonal carcinoma have been ablated by chemotherapy.

Benign Tumors Arising in Lung Parenchyma

Mucinous Cystadenoma of Lung

Mucinous cystadenoma of lung is an extraordinarily rare lesion, typically sharply demarcated from the surrounding peripheral lung parenchyma by a fibrous capsule that encloses locules of viscous mucinous material, the locules being lined by benign-appearing mucin-producing epithelial cells. Absence of invasion is a prerequisite for the diagnosis, and this tumor requires distinction from mucinous (colloid) adenocarcinoma of lung.

Alveolar Adenoma

Benign alveolar adenoma of lung is a rare entity, most often discovered incidentally in chest radiographs taken for other reasons (Figure 6). These lesions are usually encountered in middle adult life, and in females more often than males. The
predominant localization of alveolar adenoma to the left lower lobe as seen in Figure 6 (about 60% of cases) is unexplained.

These lesions represent well-demarcated but unencapsulated microcystic tumors that recapitulate the structure of the alveolar septum, with a lining of pneumocytes and variable amounts of underlying fibrovascular tissue (Figure 7). Typically, the lining epithelium displays reactivity for thyroid transcription factor-1 (TTF-1), surfactant apoprotein, cytokeratins, and carcinoembryonic antigen. The prognosis for these tumors following surgical resection is excellent. Lymphangioma is the main differential diagnosis and one case of alveolar adenoma has been reported as such in the literature.

So-Called Sclerosing Hemangioma

Although the term ‘pneumocytoma’ has been proposed as an alternative to ‘sclerosing hemangioma’, the latter term is well entrenched (‘pneumocytoma’ would also invite confusion with alveolar adenoma).

Typically, sclerosing hemangioma of lung is asymptomatic at the time of detection (only about 20% have respiratory symptoms that can include cough, hemoptysis, or chest pain). Sclerosing hemangioma can arise in any of the lobes of lung, and involvement of large airways and pleura can occur but is rare (about 1% of cases). Sclerosing hemangiomas have been recorded from early childhood through to old age, and females predominate over males. The tumor seems to occur with particular frequency in East Asia, for reasons that are unexplained.
Usually, most sclerosing hemangiomas are less than 30 mm in diameter, and characteristically they comprise angiomatoid and hemorrhagic foci in association with stromal sclerosis, papillary structures covered by epithelioid cells (Figure 8), and other areas that consist of sheets of epithelioid cells. Although the genesis or pattern of differentiation for sclerosing hemangioma remained uncertain for many years, more recent studies reveal that the pattern of differentiation is that of embryonic alveolar epithelium (with positive labeling for TTF-1, although only the better-differentiated papillary areas usually show positive reactivity for surfactant-specific apoprotein).

Benign Clear-Cell Tumor of Lung (‘Sugar’ Tumor)

First described by Liebow and Castleman in 1963, benign clear-cell tumor (CCT) of lung is a rare neoplasm, typically discovered in chest radiographs taken for other reasons.

CCT usually comprises sheets of cells with eosinophilic to clear cytoplasm, with gaping blood vessels devoid of smooth muscle and which are often hyalinized (Figure 9) – a point of distinction from primary or secondary clear-cell carcinomas such as metastatic renal cell carcinoma.

The histogenesis and pattern of differentiation in CCT remained elusive for many years, but recent studies indicate that these lesions show immunoreactivity for markers of melanocytic differentiation (such as HMB45 and melan A) and melanosomes have been found in some cases on electron microscopy (Figure 10). It has been proposed that CCT represents a member of the PEComas: a group of tumors related to perivascular epithelioid cells (PECs), whose other members include LAM, micronodular pneumocyte hyperplasia in some patients with tuberous sclerosis, and angiomyolipoma of the kidney and other sites (which include lung on very rare occasions). Whether the PEComa concept will
prove any more valid or useful than the neurocristopathies is open to doubt, and the normal cell counterpart for the PEComas is yet to be identified.

**Inflammatory Myofibroblastic Tumor**

Inflammatory myofibroblastic tumor (IMFT) exemplifies the problem of delineation of the borderland between benign tumors of the lung and pleura versus inflammatory disorders and low-grade malignant lesions; the time-honored term ‘inflammatory pseudotumor’ and the alternative expression ‘plasma cell granuloma’ imply that these lesions are non-neoplastic. However, there appears to be an emerging consensus that the fibrohistiocytic subtype of IMFT represents a neoplastic lesion, whereas the plasma cell granuloma subtype probably represents a non-neoplastic lesion of unknown and perhaps variable causation.

IMFT occurs with about equal frequency in both sexes, and from early childhood to late adult life, but with a peak incidence in middle adult life. Typically, patients present with cough, hemoptysis, dyspnea, or chest pain, while other lesions are asymptomatic at the time of detection. Typically, IMFT is a solitary sharply demarcated mass lesion (Figure 11), but multifocal lesions are well recognized. The tumors have diameters usually in the range of about 5–300 mm, located within the lung parenchyma, but involvement of bronchial structures can occur, as can extension into pulmonary vessels.

The fibrohistiocytic variant of IMFT also requires distinction from the cystic fibrohistiocytic tumor of lung (which in turn requires distinction from cystic change in pulmonary metastases from malignant fibrous histiocytomas of soft tissue).

When IMFTs have been observed in serial chest radiographs before surgical resection, they have been found to remain stable or increase slowly in size, and spontaneous resolution has been reported. However, other cases have been recorded that recur and progress, and in such cases the use of corticosteroids has been advocated. The recurrence rate for IMFT is about 25%, but substantially less than 1% metastasize. The dividing line between benign IMFT versus equivalent low-grade recurrent and malignant lesions remains ill-defined.

**Benign Meningeal Tumors and Tumor-Like Lesions of Lung**

The vast majority of meningiomas occur along the neuraxis and less commonly in the skin, but primary intrapulmonary meningiomas are well recorded (the diagnosis requires exclusion of metastatic meningioma on clinical grounds). Primary meningiomas usually show meningothelial, transitional, or fibrous patterns indistinguishable from meningiomas found in the neuraxis.

Although primary pulmonary meningiomas are exceedingly uncommon, the so-called minute meningothelioid nodules (MMTNs) are well recognized in the lung; in the past, these lesions were designated as minute pulmonary chemodectomas, but ultrastructural studies have demonstrated conclusively that these lesions are unrelated to chemoreceptor tissue and instead have interdigitating processes akin to neuraxial meningiomas. In general, MMTNs represent subclinical incidental findings in lung tissue resected for other reasons, but they are occasionally detectable in high-resolution CT (HRCT) scans, and the authors have encountered one such case where HRCT demonstrated multiple small nodules within the lungs, raising the differential diagnosis of small metastatic deposits.

Typically, MMTNs comprise microscopic nodules of uniform-appearing epithelioid cells, closely associated with venules (Figure 12).

In some instances, they are associated with cardiac failure or lung disorders of diverse type. They require no treatment, but they have been invoked as a potential precursor for primary pulmonary meningiomas (raising in turn the question of the histogenesis of MMTNs).

**Benign Tumors That Can Affect Both Pleura and Lung**

**Solitary Fibrous Tumor**

Although the great majority of solitary fibrous tumors (SFTs) affect the pleura and especially the visceral pleura, intrapulmonary SFTs are well described, as are the ones arising in sites outside
pleuropulmonary tissues. In the past, SFTs were designated as fibrous mesotheliomas, inviting confusion with the sarcomatoid and desmoplastic varieties of malignant mesotheliomas, so the expression fibrous mesothelioma for these lesions should be abandoned. Typically, SFTs affecting the pleura or lung are asymptomatic and are found in chest radiographs taken for other reasons; however, when large, SFTs can produce compression of the lung, with dyspnea and cough, and on rare occasions SFTs can result in hypoglycemia related to the production of IGF by the tumor, or hypertrophic osteoarthropathy. SFTs affecting the pleura are uncommon, and it has been estimated that about two pleural mesotheliomas are encountered in everyday surgical pathology practice for every SFT. Typically, SFTs are found during adult life and they vary in size from about 10 mm to 350 mm.

The most usual gross appearance for benign SFT is that of a pedunculated lesion localized to the visceral pleura (Figure 13). On histological examination, SFTs can show a variety of configurations, ranging from a so-called patternless pattern (Figure 14), to storiform, herringbone, and angiofibromatoid patterns. On immunohistochemistry, they are usually positive for CD34, bcl-2, and CD99, and they consistently lack cytokeratin expression (a point of distinction from most sarcomatoid mesotheliomas). A variety of cytogenetic aberrations has been recorded in SFTs, none of which appears to be specific.

In the majority of cases, SFTs are benign, but malignant SFTs are also well recognized. The criteria for discrimination between benign versus malignant SFTs remains somewhat unclear; in one study of over 220 SFTs, it was observed that no clear histological discriminator for the assessment of malignancy existed, and the criteria for malignancy in this study arbitrarily included nuclear atypia and pleomorphism, and more than four mitotic figures per 10 high-power fields, together with necrosis and hemorrhage. However, only a little over 50% of the lesions with these features pursued an aggressive course in terms of recurrence, metastasis, or both, and 45% were apparently cured by surgical resection. In another study of 50 cases, the authors felt that the most reliable indicators of malignancy were metastasis, invasion, size, and necrosis. However, as with gastrointestinal stromal tumors, such guidelines – although useful in many cases for the purposes of follow-up and management – have their limitations. The authors have encountered one case of malignant SFTs remaining somewhat unclear; in one study of over 220 SFTs, it was observed that no clear histological discriminator for the assessment of malignancy existed, and the criteria for malignancy in this study arbitrarily included nuclear atypia and pleomorphism, and more than four mitotic figures per 10 high-power fields, together with necrosis and hemorrhage. However, only a little over 50% of the lesions with these features pursued an aggressive course in terms of recurrence, metastasis, or both, and 45% were apparently cured by surgical resection. In another study of 50 cases, the authors felt that the most reliable indicators of malignancy were metastasis, invasion, size, and necrosis. However, as with gastrointestinal stromal tumors, such guidelines – although useful in many cases for the purposes of follow-up and management – have their limitations. The authors have encountered one case of malignant
SFT devoid of nuclear atypia, mitotic activity, or necrosis, but which nonetheless invaded lung and pleura, with a massive recurrence following surgical resection, and death of the patient within 10 months of diagnosis. Although some authors suggest that all SFTs should be regarded as borderline tumors, it is probably safe to emphasize that small pedunculated SFTs attached to the visceral pleura are likely to be benign, with only a low risk of recurrence following complete surgical resection (including the base of the pedicle), whereas large sessile SFTs affecting the parietal pleura and especially those which show obvious necrosis, should be regarded as having a high potential for malignant behavior.

Pleuropulmonary Thymoma

The occurrence of primary pleural thymomas is now well established, and rare cases can occur within the lung. One essential criterion for the diagnosis of such cases is exclusion of a primary thymic thymoma. The histological appearances of the pleuropulmonary tumors differ in no way from primary anterior mediastinal thymomas.

Benign Tumors of the Pleura

Benign Adenomatoid Tumor of the Pleura

Benign adenomatoid tumors of the pleura are exceedingly rare. The histological appearances are essentially identical to those of extrapleural benign adenomatoid tumors affecting the genital tract. Typically, these rare lesions represent small incidental lesions found at thoracotomy carried out for other reasons. They require discrimination from malignant mesotheliomas of epithelioid type with a prominent adenomatoid pattern.

Multicystic and Well-Differentiated Papillary Mesothe-lioma

In contrast to multicystic and well-differentiated papillary mesotheliomas (WDPMs) affecting the peritoneum, such lesions in the pleura are exceedingly rare, and we have encountered only a single case of a pleural multicystic mesothelioma (defined as such because of gross cystic spaces containing thin serous fluid as opposed to a microcystic architecture found in conventional malignant epithelioid mesotheliomas).

In the peritoneum, solitary WDPMs are regarded as benign, whereas multifocal lesions of this type are sometimes considered to be borderline neoplasms with a protracted and indolent natural history. The occurrence of WDPM in the pleura is less well established than for the peritoneal counterpart, but such lesions have been recorded. However, conventional malignant epithelioid mesotheliomas can have an extensive papillary architecture that may not be sampled by a small biopsy, so that accurate identification of these lesions in the pleura can be beset with uncertainty, and an aggressive clinical course would indicate this happenstance. Diagnosis of benign WDPM affecting the pleura preferably requires local removal of the entire lesion, which consists of delicate to club-shaped papillary processes covered by a single layer of cuboidalized mesothelial cells, with no evidence of invasion of the sublesional tissues.

Calcifying Fibrous Tumor of the Pleura

Calcifying fibrous (pseudo-)tumor of the pleura is an exceedingly rare lesion described only in adults. CT scans have demonstrated well-demarcated and partly calcified nodular lesions affecting the pleura. These lesions comprise hypocellular benign-appearing fibrocollagenous tissue with rounded (psammoma-like) calcific bodies (Figure 15). Immunohistochemical studies have shown positive labeling for vimentin and CD34 positivity in scattered cells, along with actin and desmin, and a relationship to inflammatory myofibroblastic tumor has been invoked. Follow-up has been entirely benign.

See also: Antiviral Agents. Mesothelioma, Malignant. Tuberous Sclerosis.

Further Reading

Overview

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Abstract

Although the most common malignancies of the lung are primary bronchogenic carcinomas and metastatic tumors, a wide range of rarer tumor types can occur in humans. Newer techniques to establish histological confirmation of malignancy include the use of ultrasound and fluorescence to enhance the precision of bronchoscopic biopsy. Needle aspiration of lung lesions can also be of high diagnostic yield. Certain tumor types can now be differentiated using new immunohistochemical markers, although tumor heterogeneity and sampling issues can occasionally influence the accuracy of the final diagnosis. The varying susceptibilities of cigarette smokers to developing bronchogenic carcinoma appear increasingly likely to be related to mutations at multiple genetic loci and their interactions. Recent advances in imaging techniques such as positron emission tomography, computed tomography densitometry, perfusion CT algorithms, and magnetic resonance imaging are increasing the accuracy of pretreatment staging and also improving the overall functional assessment of patients.

Introduction

There are a large number of malignant tumors that affect the lungs, ranging from metastatic malignancies to the most common type, bronchogenic carcinoma (see Tumors, Malignant: Bronchogenic Carcinoma). Bronchogenic cancers can also metastasize to the lungs, as well as to other sites; this subject is covered elsewhere in this encyclopedia (see Tumors, Malignant: Metastases from Lung Cancer). Other primary cancers arising within the chest include tumors of lymphoid origin (see Tumors, Malignant: Lymphoma), vascular/blood origin (see Tumors, Malignant: Hematological Malignancies), and rare tumors (see Tumors, Malignant: Rare Tumors). Metastatic cancers can involve the lung parenchyma, the lymph nodes (see Tumors, Malignant: Carcinoma, Lymph Node Involvement), or other thoracic structures.

Thus, the usual clinical challenge when faced with the possibility of cancer in the lung is to ascertain firstly the presence of malignancy, secondly the origin of the cancer, and finally the extent or stage of cancer so that therapy may be appropriately individualized. In future, this challenge may be magnified if low-dose helical computed tomography (CT) scanning is shown from randomized trial data to be effective in reducing lung cancer mortality. This technique has already been shown to be severalfold more sensitive than conventional chest radiography for detecting pulmonary nodules. Indeed, studies to date show that low-dose CT scanning can potentially detect a large number of pulmonary nodules in at-risk populations. Most of these pulmonary nodules turn out not to be malignant but require further evaluation using a variety of follow-up algorithms or invasive investigations.