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Approach to Peribronchovascular Disease on CT

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Diseases that are predominantly peribronchovascular in distribution on computed tomography by definition involve the bronchi, adjacent vasculature, and associated lymphatics involving the central or axial lung interstitium. An understanding of diseases that can present with focal peribronchovascular findings is useful for establishing diagnoses and guiding patient management. This review will cover clinical and imaging features that may assist in differentiating amongst the various causes of primarily peribronchovascular disease. *Semin Ultrasound CT MRI 40:187-199 © 2018 Elsevier Inc. All rights reserved.*

Diseases that are primarily peribronchovascular in distribution represent an identifiable pattern on computed tomography (CT) and include those entities that primarily localize either to the airways, vasculature and/or associated lymphatics within the central or axial interstitium.^{1,2} To date, interstitial lung diseases have been approached through CT pattern recognition, for which algorithms have been proposed including those defined by diffuse nodular, reticular, or overall increased or diminished lung opacity, respectively.³

Our discussion will concentrate upon peribronchovascular disease centered around and primarily affecting the axial interstitium. This involves diseases presenting as combinations of nodules, masses and/or focal ground-glass attenuation or air-space consolidation that have in common the resulting appearance of air-bronchograms. Based on these characteristics, an algorithm is introduced that integrates characteristic CT findings and essential critical clinical features that provide a limited differential diagnosis.

Lung Interstitium and Peribronchovascular Disease

An understanding of the axial interstitium and its role in defining the CT appearance of peribronchovascular disease is the key to interpretation. The axial interstitium is comprised of a fine network of connective tissue that provides the lattice upon which the central airways, vasculature, and lymphatics course and extend from the hila throughout the lungs.

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Although still of debate, recent publications have supported that the interstitium, rather than containing dense connective tissue only, also has spaces that are compressible and distensible and defined by the network of collagen fibers.⁴ Through confocal microscopy, investigators have shown collagen bundles interspersed with spaces such as bilary submucosa.

Disease Associated with Peribronchovascular Predisposition

Peribronchovascular diseases originate from the axial interstitium and bronchus-associated lymphoid tissue that surround the bronchi and extend into lung periphery. We will consider peribronchovascular abnormalities to be primarily within the inner two-thirds of the lung. The focus of this description will be on larger nodules and consolidations, rather than diffuse small nodules for which alternate diagnostic algorithms are available.

Pulmonary Lymphoma and Lymphoproliferative Disorders

Lymphoma

Lymphoma in the lung can be either secondary or primary. The World Health Organization conducted an update in 2016 to the 2008 classification of mature lymphoid, histiocytic, and dendritic neoplasms.⁵ The classification separates these constituents into mature B-cell neoplasms, mature T and NK neoplasms, Hodgkin lymphoma, post-transplant lymphoproliferative disorders, and histiocytic and dendritic



Figure 1 64-year-old man after cardiac and renal transplantation who is chronically immunosuppressed, presented with dyspnea and weight loss. Soft tissue peribronchial nodular left lower lobe opacity (arrow) and right lower lobe ill-defined predominantly ground-glass opacity with mild consolidation. Bronchoalveolar lavage showed T-cell lymphoma, while transbronchial subcarinal lymph node biopsy showed B-cell and T-cell lymphoma in subcarinal node.

cell neoplasms.⁶ This update reflects better understanding of the precursors of leukemia and lymphoma, which may undergo observation rather than treatment, and the underlying molecular causes.

Secondary involvement of the lung by lymphoma. Secondary involvement occurs in both non-Hodgkin and Hodgkin lymphoma. Less prevalent than non-Hodgkin lymphoma, Hodgkin disease patients have lung parenchymal involvement more than their counterparts with non-Hodgkin lymphoma.^{7,8} Adenopathy in the mediastinum and hila is frequently present, such as in 67%-84% of Hodgkin lymphoma, while non-Hodgkin lymphoma has 43%.⁹ A lymphangitic carcinomatosis pattern appears on CT as thickened interlobular septa around the secondary pulmonary nodule and centrilobular core regions, related to lymphoid tissue enlargement and lymphatic infiltration. Nodularity is helpful for differentiating this from edema that occurs due to lymphatic obstruction in the hilar regions. Lung masses and nodules can occur (Fig. 1).⁷ The pleura can be affected, either by effusions or soft tissue.⁸ The degree of adenopathy in the mediastinum is a helpful feature for differentiating from primary pulmonary lymphoma.

Primary pulmonary lymphoma. Primary pulmonary lymphoma is less common, comprising less than 1% of lymphoma diagnoses. Primary pulmonary lymphoma comprises about 3%-4% of extranodal lymphomas.¹⁰ Primary pulmonary lymphoma represents a monoclonal proliferation of lymphoid tissue that arises from the lymph nodes around that bronchus and mucosa of the alveoli.¹¹ Other sites outside of the lung cannot be identified at the time of or within 3 months of presentation. Most commonly, pulmonary lymphoma derives from extranodal marginal zone lymphoma of mucosal associated lymphoid tissue (MALT), reported in

70%-90% of cases.^{12,13} Diffuse large B-cell lymphoma predominantly accounts for the remainder of primary pulmonary lymphoma. Less common entities include lymphomatoid granulomatosis, primary pulmonary Hodgkin's lymphoma, and plasmacytoma.¹⁴ Other lymphoproliferative disorders affecting the lung and pleura also include nodular lymphoid hyperplasia and Castleman's disease, which lack monoclonal proliferation, in addition to primary effusion lymphoma that affects pleural, pericardial, or peritoneal spaces in immunocompromised individuals such as with acquired immune deficiency syndrome (AIDS).¹¹

MALT lymphoma arises from tissues that typically lack MALT tissue, yet develop MALT lymphoma due to infections and inflammation, including autoimmune disease, such as in 16%.¹³ Other organs affected by MALT lymphoma are the gastrointestinal tract, thyroid gland, and salivary glands. The tumor is typically comprised of B-cells. Marginal zone lymphomas other than MALT include nodal marginal zone lymphoma and splenic marginal zone lymphoma. While *Helicobacter pylori* is associated with developing MALT lymphoma in the stomach, no conclusive organism has been identified for pulmonary MALT lymphoma.

Pathology of MALT lymphoma is that of small clonal lymphoid cells in the bronchiolar and alveolar epithelium with immunohistochemistry positive for CD20 and CD43.¹³ Approximately one-third of patients with MALT lymphoma can be asymptomatic. Patients have been described to have a mean age of 50-60 years, although ages can range from as young as 30 years to a more elderly age such as 80 years.^{13,15} An association of MALT lymphoma with autoimmune disease has been reported, with 25% of patients with pulmonary lymphoma having rheumatoid arthritis, Sjogren's syndrome, or mixed connective disorder.¹⁵ Possible mechanisms for developing lymphoma include antigenic stimulation and underlying genetic causes, such as translocations.¹³ Diffuse large B-cell lymphoma is diagnosed pathologically when large B cells in sheets are identified. Individuals with diffuse large B-cell lymphoma are symptomatic with fever, weight loss, and pulmonary symptoms.

Imaging of primary pulmonary lymphoma has been described as mass-like consolidation in 88% and nodules in 75%, with air bronchograms reported in 88% (Fig. 2).¹⁵ Peribronchovascular thickening has been reported,^{15,16} with peribronchovascular thickening identified in 7 of 9 patients in one investigation.¹⁵ Attenuation of nodules can be ground glass.¹¹ Lesions are more commonly multiple, although can be solitary.^{10,13,15} Halos of ground glass can occur around soft-tissue nodules.¹⁷ Lymphomas of large cells are reported as more mass-like and with nodules lacking air bronchograms, compared to lymphomas of small cells.¹⁰ Lymphadenopathy is not a major finding with MALT lymphoma. King et al. describe 29% of their cohort of 24 to have lymphadenopathy, 3 of which with no more than 2 nodes that were smaller than 15mm, while the 4 others had less than 20mm nodes; another investigation by Wislez et al. describe hilar nodes in two of 13 patients.^{11,15} Cavitation and necrosis is seen in large diffuse B-cell lymphoma,¹¹ and the tracheobronchial tree can be affected.¹⁸ Pleural effusions are

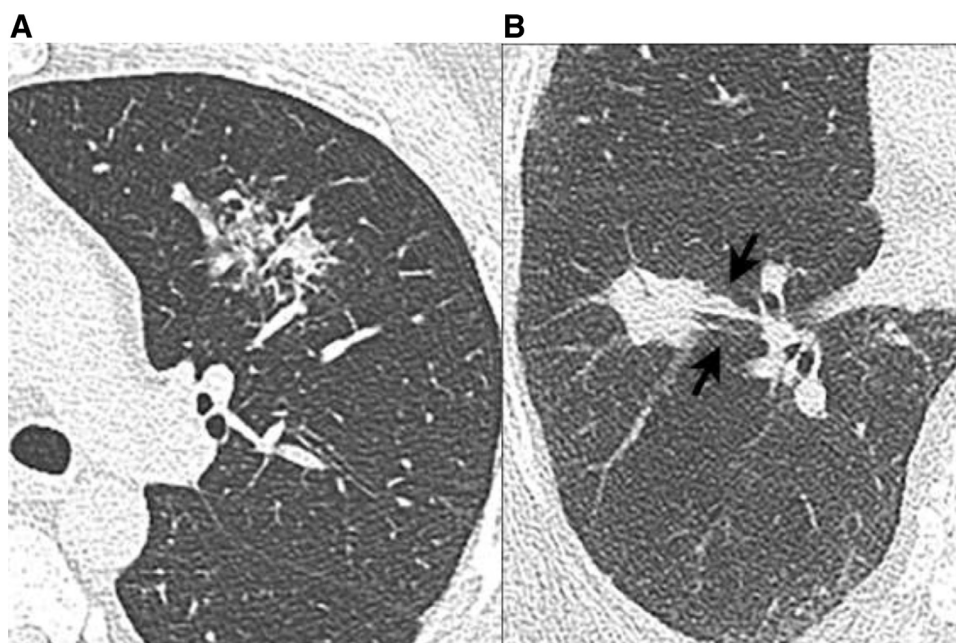


Figure 2 Primary pulmonary lymphoma. (A) 46-year-old man. Incidental soft tissue peribronchovascular focal opacity on pulmonary vein CT performed for atrial fibrillation ablation planning. Air bronchograms are present within the lesion. Biopsy revealed extranodal marginal zone B-cell MALT lymphoma. (B) 90-year-old woman with confirmed extranodal marginal zone B-cell MALT lymphoma. CT image demonstrates a soft tissue nodule centered around the bronchovascular bundle (arrows) seen entering the lesion.

identified in approximately 29% by King et al. whereas Wislez et al. report none.^{15,16}

The lactate dehydrogenase value, often considered to be elevated in lymphoma, can be normal in MALT lymphoma. As mentioned, autoimmune disease is a predisposing factor.¹³ An association of AIDS with lymphoma is known, primarily diffuse large B-cell lymphoma.^{19,20} Diagnosis of primary pulmonary lymphoma is made by open surgical biopsy, and when multifocal disease is present, transthoracic needle core biopsy/ fine needle aspiration and transbronchial biopsy with CT navigation and cryobiopsy are potential methods to make diagnosis with increasing sensitivity. Molecular testing of cells obtained from bronchoalveolar lavage fluid may aid in diagnosing MALT lymphoma.¹²

Lymphomatoid Granulomatosis

A rare entity, lymphomatoid granulomatosis is related to Epstein Barr Virus infection and comprised of large B cells. Cells test positive for Epstein Barr Virus RNA using Epstein-Barr encoding region in situ hybridization. Histopathologically, the disease is centered around the vessels and characterized by a heterogeneous polymorphous group of lymphoreticular cells that exhibit necrosis and invasion of the vessels.^{6,21} Diagnosis by pathology of lymphomatoid granulomatosis can be challenging, and the criteria have evolved over time. Therefore, cases considered lymphomatoid granulomatosis in the past may not satisfy current criteria and now are considered other lymphoproliferative disorders.

Clinically, patients can be immunocompromised, and their reported age ranges between 40 and 60 years, with a mild male predominance.^{11,22,23} The lungs are primarily

involved in about 80% of cases. Also, patients can have other organs involved, such as the brain in 30%, ear, nose and throat, skin and kidneys.^{11,24} Diagnosis is usually made by surgical lung biopsy, while bronchoscopic biopsy is not as diagnostic. Sampling of other involved sites can provide a diagnosis, such as the skin.

Lymphomatoid granulomatosis appears on CT as peribronchovascular masses that spare the lung periphery and can have air bronchograms and cavitation (Fig. 3).^{10,22,23,25} In a series by Chung et al., lesions size is 4-66 mm.²² Also, ground-glass nodules can evolve to solid masses.²⁵ Ground-glass opacity can occur around the nodules, creating a halo



Figure 3 Lymphomatoid granulomatosis. Patchy ground-glass opacities and consolidation are seen in the right lung. Additionally, soft tissue nodules, some of which have ill-defined borders are present (arrows) and are clustered.

appearance,²² and a reversed-halo sign in which ground-glass opacity centrally is surrounded by soft tissue is also a possible manifestation.²⁶ Lesions are hypermetabolic on fluorodeoxyglucose positron emission technology CT.²⁷ Small pleural effusions can occur.²²

Lymphocytic Interstitial Pneumonia and Follicular Bronchiolitis

Lymphocytic interstitial pneumonia (LIP) and follicular bronchiolitis probably relate to a spectrum of disease, with overlap in features clinically and on histology, with a more bronchiolar association for follicular bronchiolitis, whereas LIP has more diffuse infiltration of the interstitium.^{28,29} Follicular bronchiolitis is a polyclonal hyperplasia within the bronchus-associated nodal tissue. Reactive germinal centers are present.² Idiopathic follicular bronchiolitis is rare, and secondary forms are associated with autoimmune diseases such as Sjogren's syndrome, connective tissue disorders including rheumatoid arthritis, immunodeficiency that is either congenital or acquired, and interstitial lung disease. On CT imaging, poorly-defined centrilobular and subpleural nodules are more commonly seen around the bronchioles than bronchi. Although frequently small, nodules can be large in size between 3 and 12 mm with ill-defined borders.^{28,30} Patchy ground-glass opacities and, less commonly, peribronchovascular consolidation can occur.^{28,31} Adenopathy is not a frequent feature.

In LIP, a benign polyclonal proliferation of lymphocytes and plasma cells in the pulmonary interstitium is seen. LIP is also associated with patients who are immunocompromised, such as those with Sjogren's and acquired-immunodeficiency syndrome, multicentric Castleman's disease, and autoimmune diseases. LIP on CT appears as small nodules and ground glass opacity. Jokoh et al., in a series of 22 patients, report CT findings comprising ill-defined centrilobular nodules in 22, ground glass opacity in 22, bronchovascular thickening in 19, subpleural nodules in 19, septal thickening in 18, cysts in 15 (1-30mm, mean 6.4mm), and lymph node enlargement in 15.³² Large nodules on the order of 1-2cm and air-space consolidation are both described in 41% of their cohort, and enlarged lymph nodes seen in 78%.³²

Other less common entities reported are Castleman's disease, also termed angiofollicular lymph node hyperplasia, which is associated with LIP. The imaging manifestations on CT in the lung of Castleman's disease may relate to concomitant LIP.²

Lung Cancer

Adenocarcinoma is now the most common subtype of lung carcinoma. The appearance of adenocarcinoma on CT ranges from pure ground-glass nodules to part-solid and solid nodules.³³ Lung cancer patients often have a smoking history; however, nonsmokers are affected by lung cancer, some of which have underlying molecular mutations and translocations.³⁴ Other risk factors for lung cancer include occupational and environmental exposures such as to asbestos and radon. Patients with early stage lung cancer frequently

present with a lesion that is incidentally detected on a chest radiograph or CT.

Often solitary, yet potentially multiple, lung cancer is considered in the differential diagnosis of peribronchovascular lesions (Fig. 4). The presence of emphysema, bulla, and bronchial wall thickening may indicate an individual with a smoking history. Subsolid nodules well demonstrate a peribronchovascular distribution, as internal air bronchograms can be seen. When adenopathy is present in the ipsilateral hilum and mediastinum in combination with a solitary lesion, lung cancer can be considered, as other peribronchovascular abnormalities are more typically multifocal.

Organizing Pneumonia

Organizing pneumonia pathologically is characterized by fibromyxoid intra-alveolar plugs containing fibroblasts, myofibroblasts, and connective tissue matrix with foamy macrophages.^{35,36} Hyaline membranes, necrosis, vasculitis, eosinophilia or granulomatous response are lacking. A more recently described variant, acute fibrinous organizing pneumonia (AFOP) on histopathology has prominent fibrin deposition to a greater degree than with typical organizing pneumonia accompanied by with type II pneumocyte hyperplasia.^{36,37} AFOP has been described by Beasley et al. and Travis et al. in small cohorts of 11 and 10, respectively.³⁸ Another form of organizing pneumonia termed granulomatous organizing pneumonia entails non-necrotizing granulomas that are poorly-formed and accompany organizing pneumonia.

Organizing pneumonia should be the major finding on histopathology if a diagnosis of organizing pneumonia is rendered as the primary disease. Also, organizing pneumonia is often secondary to other disease processes and has been described in conjunction with infection, neoplasms, drug reaction, radiation therapy, and autoimmune disease. When no identifiable cause exists, organizing pneumonia is considered idiopathic and termed cryptogenic organizing pneumonia, which falls within the category of acute or subacute idiopathic interstitial pneumonias according to the American Thoracic Society multidisciplinary classification of interstitial pneumonias.³⁷

The typical age group affected by organizing pneumonia is approximately 50-60 years, although the age of affected individuals can vary.^{36,39} Subacute cough, dyspnea, wheezing, and fatigue on the order of 3 months or shorter are presenting features, with fever more common with AFOP.³⁶ AFOP has been associated with a worse prognosis. Organizing pneumonia is a common pattern on CT identified with immunotherapy for cancer.⁴⁰

Organizing pneumonia appears as consolidation and ground-glass opacities. A peribronchovascular and/ or subpleural distribution is reported in approximately 53%-63% of patients with cryptogenic organizing pneumonia (Fig. 5).^{39,41} Consolidation can be peripheral in 27%, as reported by Chung et al.⁴² An atoll or reversed-halo sign can occur, seen as a nodule with central lower-attenuation ground-glass and peripheral soft-tissue opacity. In patients with organizing



Figure 4 Lung adenocarcinoma. A soft-tissue spiculated mass containing air bronchograms is detected incidentally in an HIV-positive woman with renal failure. On coronal (A) and axial (B) CT images, the mass is centered around bronchovascular bundles, and the center of the finding is within the inner two-thirds of the lung.

pneumonia, a reversed-halo sign was initially described in one-fifth of patients in a series.⁴³ Subsequently, a number of etiologies known to cause a reversed-halo sign and include infection such as zygomycosis, invasive aspergillosis, tuberculosis, histoplasmosis, cryptococcosis, *Pneumocystis jirovecii* pneumonia, paracoccidioidomycosis; infarct from pulmonary embolism; eosinophilic processes; post-lung ablation and stereotactic body radiation therapy changes; lung adenocarcinomas; granulomatosis with polyangiitis; lymphoproliferative

disorders; and sarcoidosis.^{44,45} Pleural effusions are not frequent.^{36,46} Thus, integration with other clinical and imaging features is needed when seeing the reversed-halo sign.

The relationship of cryptogenic organizing pneumonia to nonspecific interstitial pneumonitis (NSIP) has been suggested by imaging investigations. Lee et al. also evaluated the evolution of findings with complete resolution identified in 27%. A decrease was noted in 68% and no change was observed in 1 patient (5%) in their cohort during the follow-up period.

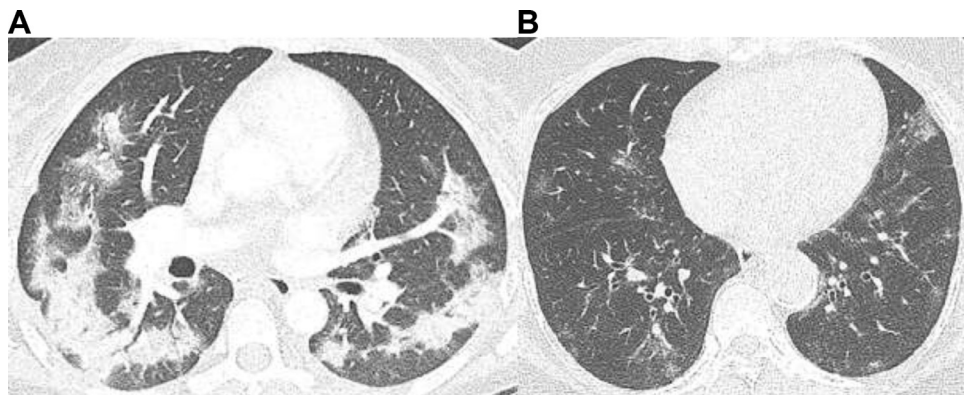


Figure 5 Organizing pneumonia. (A) A woman with gastrointestinal stromal tumor has a history of yttrium-90 (Y-90) therapy for liver metastasis and known shunting of Y-90 to the lungs. The predominantly peripheral consolidation spares the subpleural region and is associated with bronchovascular structures, such as in the right middle lobe and lingula. Organizing pneumonia, confirmed by wedge resections, is attributed to radiation pneumonitis. (B) CT image of a 44-year-old woman with muscle-biopsy proven dermatomyositis and pathologically confirmed bronchiolocentric organizing pneumonia. The lower lobe predominant ground glass nodules are associated with bronchovascular regions.

Patients with unresolving parenchymal opacities have worse pulmonary function tests such as forced vital capacity and diffusion capacity; more diffuse consolidation; and longer treatment duration.^{39,42}

Organizing pneumonia in some patients is shown to progress to fibrosis (progressive interstitial fibrosis) that resembles on histopathology NSIP.³⁷ Imaging studies support the evolution of organizing pneumonia to persistent CT findings, with an appearance similar to fibrotic NSIP.^{39,42} In one investigation by Chung et al., a NSIP-like pattern is identified in 74% of patients with nonresolving organizing pneumonia.⁴²

Infection

Peribronchovascular consolidation and ground-glass opacities are seen in bacterial, viral, and fungal infections.⁴⁷⁻⁵⁰ Parasitic infection such as schistosomiasis is another potential etiology. Generally, infection derives from the large and small airways, affecting the adjacent alveoli. Spread can occur to other areas of the lung. In terms of bacterial agents, a large number of organisms lead to bronchopneumonia, such as *Staphylococcus* species and gram negative organisms that are either community or hospital-acquired. Active tuberculosis also causes bronchopneumonia.

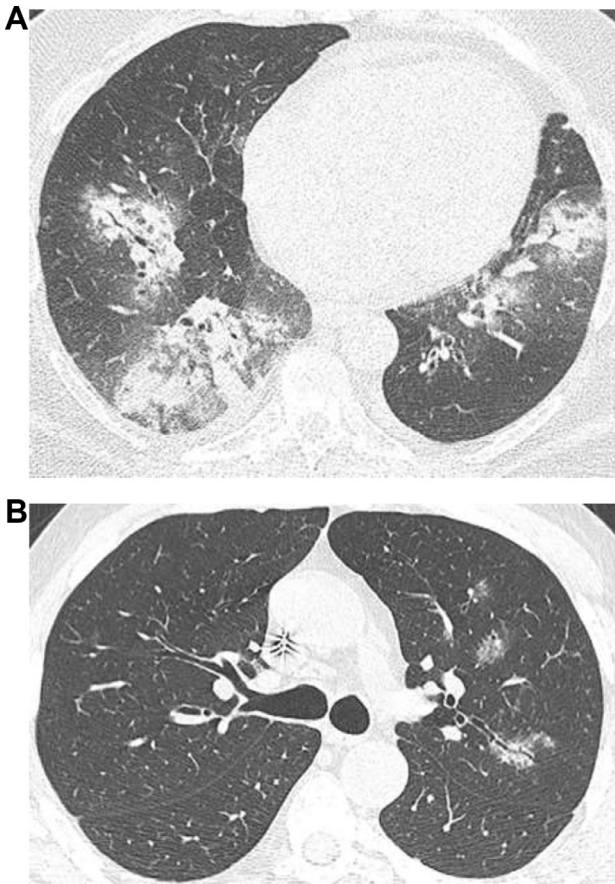


Figure 6 Bronchopneumonia in two different patients. Focal areas of consolidation (A) and nodular ground glass and soft tissue opacities (B) surround the bronchovascular regions. A right pleural effusion (A) is present.

Viruses such as cytomegalovirus (CMV), adenovirus, herpes simplex virus, human metapneumovirus, human parainfluenza virus, respiratory syncytial virus, and influenza lead to pneumonia.^{47,51,52} Clinical features of viral pneumonia include upper respiratory symptoms, fever, sore throat, and dyspnea and hypoxemia. Patients who are immunocompromised such as due to steroids or organ and hematopoietic stem cell transplantation are highly susceptible to atypical viral infections. Bone marrow transplant patients are vulnerable to CMV infections due to reactivation of CMV in previously infected patients, occurring most commonly in the early phase or less than 100 days after transplantation (50%-70%) but also in the late phase, reported in 31%.⁵³

Fungal infections can be opportunistic such as aspergillosis and mucormycosis, in addition to endemic in etiology including paracoccidioidomycosis, blastomycosis, coccidioidomycosis, and histoplasmosis. *Aspergillus* infection affects immunocompromised patients, such as those on steroids, leukemia, and after bone marrow and organ transplantation, often in the form of angioinvasive aspergillosis (ANG), although airway invasive aspergillus (AIA) is another manifestation that is associated with peribronchial opacities.^{49,54} In heart transplantation patients, the authors of one study report about 37% of invasive aspergillus infections to be related to AIA, and patients have worse prognosis than counterparts with ANG.⁵⁵ Mucormycosis also affects immunocompromised patients, with a higher incidence of rhinocerebral involvement than with invasive aspergillosis, and leads to peribronchial opacities on CT.⁵⁶ Paracoccidioidomycosis, also known as South American blastomycosis, is the most common endemic fungal infection in South America.⁵⁷ Funari et al. describe that 78% of their patients have peribronchovascular thickening and 34% ground-glass opacities with consolidations, cavitation, and nodules.⁵⁷

On imaging, infection particularly with bacterial agents appears as a bronchopneumonia, with peribronchovascular consolidations and ground-glass opacity, given the dissemination via the airways (Fig. 6). Accompanying bronchiolitis is often present and seen on CT as small centrilobular tree-in-bud nodules that represent inflamed and infected small airways at the terminal respiratory bronchiole level. Cavitation can occur particularly with bacterial and fungal infections. Viral infections affect the lung interstitium and present on CT with centrilobular nodules, ground-glass opacity, consolidation, and bronchial wall thickening (Fig. 7). Commonly, viral infections are bilateral and diffuse with asymmetric distribution. Some viruses are associated with pleural effusions.⁵⁸ Fungal infections are often multifocal, presenting with mass-like consolidations and large nodules, although can be solitary. In one study, AIA is reported as having a higher number of patients with peribronchial distribution, while ANG had more cavitory nodules.⁵⁵ A halo of ground-glass opacity around a nodule is a sign of ANG in the early phase. Subsequent development of a crescent of air (air-crescent sign) occurs within the lesion often, once the immunity of the affected patient is restored and a white-cell response to the infection can occur.⁵⁹



Figure 7 Human metapneumovirus pneumonia. 86-year-old man presented with wheezing and fever and was diagnosed by molecular testing. Patchy ground-glass opacities in the right lower lobe are centered around the bronchovascular bundles, and mild clustered nodules are present. Bilateral mild ground-glass opacities are present.

Diagnosis of infection entails integration of clinical, laboratory, and imaging findings. A clinical suspicion of infection, typically indicated by fever, shortness of breath, and cough in an acute and subacute presentation, in conjunction with a peribronchovascular distribution raises suspicion for infection from bacterial, viral, and, particularly in immunocompromised patients or in an area where endemic fungal infections are prevalent, fungal etiologies. A more chronic clinical history raises question of mycobacteria and endemic fungal etiologies.

When infection is suspected, noninvasive tests including sputum analysis for smear and culture can be performed in addition to other laboratory workup entailing a white blood count and differential. Antigen urine testing for community-acquired pneumonia for *Streptococcus pneumoniae* and *Legionella pneumophila* are available; although, in conjunction with sputum analysis and two blood cultures, these tests are less than 50% sensitive.⁶⁰ A number of rapid molecular testing options such as nucleic acid amplification tests and polymerase chain reaction (PCR) have been developed to improve the diagnosis of infection in patients who are critically ill. These new methods can be performed on nasal and nasopharyngeal swabs and sputum. Agents such as *Staphylococcus aureus*; *Streptococcus pneumoniae*; a large number of viruses that include adenovirus, parainfluenza, respiratory syncytial virus, human metapneumovirus, coronavirus, rhinovirus; *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae* can be assessed for using molecular testing.^{60,61} The addition of molecular testing increases the diagnosis of pathogens causing severe community-acquired pneumonia to 70%-80%.⁶⁰ Procalcitonin has been investigated as a method to detect and differentiate bacterial and mixed bacterial/viral infections from only viral infection, which does not have procalcitonin levels higher than 0.25 ng/ml. The combination of procalcitonin and viral PCR analysis can be used to identify patients with community-acquired pneumonia.⁶⁰ However, caution is needed given procalcitonin levels can be negative for a few hours after bacterial

invasion and be influenced by a number of factors, such as renal failure and dialysis. CMV infection is established when peripheral antigenemia for CMV is identified, or tissue that is sampled is positive for CMV.⁵³ Rapid nucleic acid amplification test techniques are also available for confirming active tuberculosis.⁶² Galactomannan antigen assays from bronchoalveolar lavage and serum can be used to diagnose ANG in the acute setting, with lower sensitivity when testing serum for chronic aspergillus infection.⁶³ Beta-D-glucan assays from serum can be used to diagnose a number of fungal infections including *Aspergillus*, candida, and endemic fungi, although sensitivities vary and range between 38% and 100% depending on assay, population, and organism.^{64,65} Assays for Immunoglobulin (Ig) G that are specific for *Aspergillus* are also used to aid in diagnosing infection.⁶⁵ More invasive testing includes analysis of bronchoalveolar lavage samples for smear and culture and biopsy for verifying viral and fungal infections.

Vasculitis and Pulmonary Hemorrhage

Lung parenchymal abnormalities can be caused by small and medium-vessel vasculitis and pulmonary hemorrhage. Peribronchovascular abnormalities have been described in antineutrophil cytoplasmic antibody-associated vasculitides (ANCA) such as granulomatosis with polyangiitis (GPA), Churg-Strauss vasculitis, and microscopic polyangiitis (Fig. 8).⁶⁶⁻⁶⁸ Vasculitis can be due to: (1) collagen vascular diseases such as systemic lupus erythematosus, rheumatoid arthritis, and sarcoid; (2) a probable cause such as infection and drug reactions; (3) pauci-immune pulmonary vasculitis; (4) immune-complex small-vessel vasculitis such as Goodpasture's syndrome (antiglomerular basement membrane disease), IgA vasculitis, cryoglobulinemic vasculitis or hypocomplementemic urticarial vasculitis; and (5) IgG-4 related vasculitis. Multisystem organ involvement is present often in vasculitis. Idiopathic pulmonary hemosiderosis is a cause of pulmonary hemorrhage in the absence of vasculitis.

GPA affects patients on the order of 1 in 100,000, primarily between 30 and 50 years of age, who can have upper and lower airway involvement and glomerulonephritis that are often acute.^{66,69} Limited GPA can occur, in which renal involvement is not present and mainly the upper airways are affected.⁷⁰ Upper airway abnormalities occur in 70%-100% and include sinusitis, ear inflammation, and subglottic stenosis. Patients may present with massive hemoptysis.⁷⁰ On CT, multiple nodules and masses are present.⁶⁹ Although reported as predominantly subpleural in 89% of patients, nodules can occur in a peribronchovascular distribution in 41% (Fig. 8).⁷¹ The halo sign is reported in the series by Lee et al. in 15%.⁷¹ Adenopathy is less common, on the order of 20%.⁶⁸ Tests for cytoplasmic ANCA are highly positive on the order of 90% and have a high positive predictive value for GPA.⁷⁰ Pleural effusions are reported in 13%⁷¹ and 19%⁷² and were small and bilateral. Pleural effusions may relate to renal failure.

Eosinophilic granulomatosis with polyangiitis, also known as Churg-Strauss vasculitis, is characterized by asthma, sinus involvement, lung opacities, eosinophilia larger than

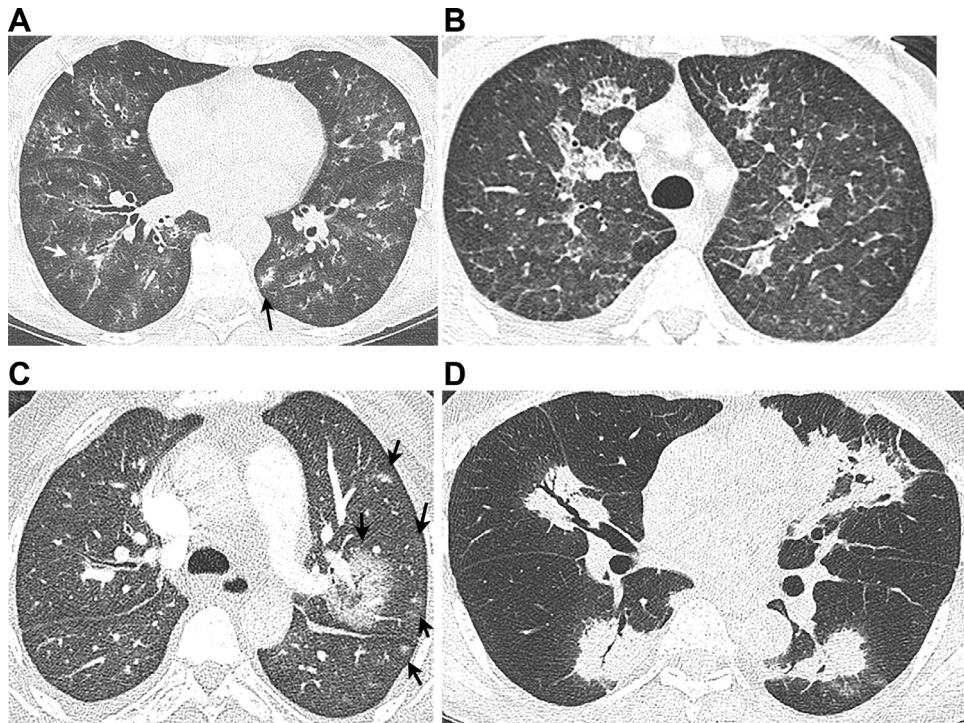


Figure 8 Vasculitis. Pulmonary hemorrhage related to P-ANCA vasculitis (A, B) in a 65-year-old woman with hemoptysis. (A) Ill-defined ground glass areas (white arrows) centered along bronchovascular bundles and soft-tissue patchy focal areas (black arrow) are present. (B) Soft-tissue patchy areas are also seen on follow-up CT in upper lobes. (C) 33-year-old woman with SLE vasculitis with soft tissue central mass-like consolidation, with central ground-glass (reversed-halo) appearance, and subsolid nodules (arrows) that improve with increasing immunosuppression. (D) IgG-4 related vasculitis diagnosed by wedge resection in a 70-year-old immunocompromised man with weight loss and dyspnea on exertion.

$1.5 \times 10^9/L$ or 10% on white blood cell differential, mononeuropathy or polyneuropathy, skin rash, cardiac disease, and eosinophilic tissue with granulomatous inflammation.^{73,74} Three phases have been described, the first being asthma, followed by a second of peripheral and tissue eosinophilia, and the third a vasculitis phase.⁷³ The eosinophilia of Churg-Strauss is higher than that of eosinophilic asthma, which is typically less than $0.8 \times 10^9/L$.⁷³ Imaging studies report parenchymal consolidations and nodules.^{75,76} In a study of CT histopathology correlation by Kim et al., consolidation in Churg-Strauss patients correlates with eosinophils in the alveoli and alveolar walls.⁶⁷ A peripheral distribution is more commonly identified.⁷⁵ Bronchial wall thickening and peribronchial thickening are identified⁷⁵ in addition to peribronchial consolidation.⁷³ In the study by Kim et al., necrotizing granulomas and areas of necrotizing vasculitis on histopathology in Churg-Strauss are seen in the peribronchial interstitium.⁶⁷ Small centrilobular nodules also are present. Interlobular septal thickening is reported to correlate with eosinophilia and fibrosis on pathology.^{75,77} Pleural effusions can occur.

A newer diagnosis, IgG4-related lung disease can result in lung disease, although limited information currently exists pertaining to the imaging findings. IgG4-related lung disease entails lymphoplasmacytic infiltration with fibrosis. Multiple other organs are involved such as the pancreas, salivary glands, kidneys, and aorta, followed by the lung.⁷⁸ Ground-glass opacity with thickened bronchial walls/bronchovascular

bundles are described (Fig. 8).^{78,79,80} Adenopathy can occur such as in 46% of patients in one study.⁸⁰

Microscopic polyangiitis, a small vessel vasculitis, presents with pulmonary hemorrhage. Multiple organs are affected, including the kidneys, lung, and skin.⁶⁶ Also, hemorrhage that tracks along the hilar structures from the mediastinum and into the lung parenchyma along the peribronchovascular bundles can lead to peribronchial ground-glass opacity.⁸¹

Eosinophilic Pneumonia

Eosinophilic lung disease can be idiopathic or secondary, such as from a drug reaction, parasites, and associated with vasculitis. Idiopathic eosinophilic pneumonia can be categorized as simple, acute, or chronic. Simple eosinophilic pneumonia is often transient and manifested by fleeting focal ill-defined opacities and peripheral eosinophilia. Acute eosinophilic pneumonia presents in an acute presentation with diffuse alveolar damage and diffuse ground-glass opacities that mimic acute respiratory distress syndrome on imaging. Peripheral eosinophilia may be lacking although eosinophils identified on bronchoscopy. Chronic eosinophilic pneumonia affects elderly patients, with greater preponderance for women. An association with asthma, a chronic clinical history of symptoms on the order of months, and peripheral eosinophilia are described.⁸² A predominantly peripheral consolidative process on CT, chronic eosinophilic

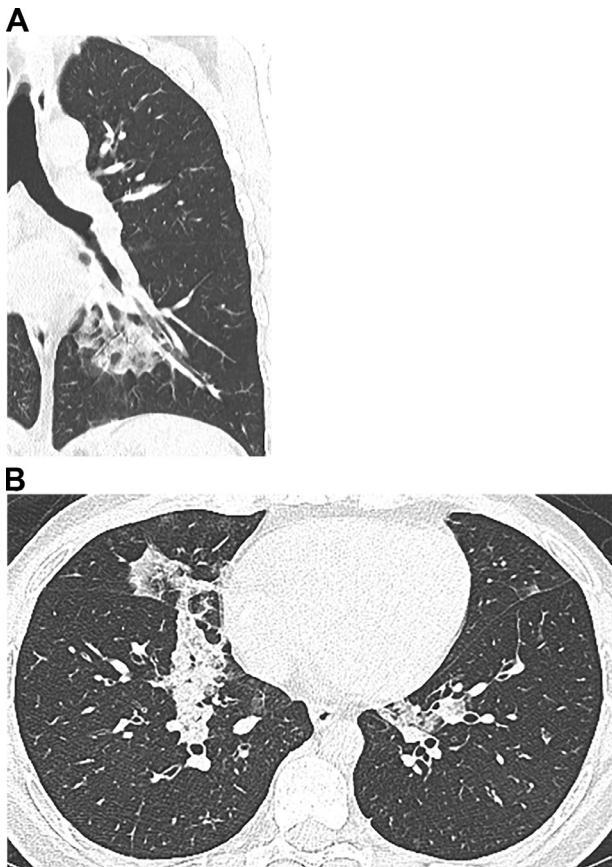


Figure 9 Chronic eosinophilic pneumonia. Man with history of eosinophilia with history of recurrent cough, wheezing. Eosinophilic pneumonia with organizing pneumonia was diagnosed on wedge resection.

pneumonia manifest as air-space nodular opacities. A peribronchial distribution is possible, such as in 9.3% of patients, as reported by Arakawa et al. (Fig. 9).⁸³ Pleural effusions are uncommon, on the order of 10%.⁷⁶

Sarcoidosis

Sarcoidosis, a granulomatous disease, can affect the lungs, appearing as a large number of small nodules in a perilymphatic distribution affecting the peribronchovascular and subpleural regions. Consolidative opacities can result from confluent granulomas termed “alveolar sarcoid.” The consolidative opacities, given the lymphatic involvement by the disease, are often peribronchovascular (Fig. 10). Individuals with sarcoid have bilateral, symmetric adenopathy in addition to calcified lymph nodes, which can be peripherally calcified. Patients are often younger in age, on the order of 30-40.⁸⁴ Skin involvement can be present. Angiotensin converting enzyme elevation occurs in approximately 75% of sarcoidosis although can be falsely positive.⁸⁵ Also elevated calcium levels can be identified.

Kaposi’s Sarcoma and Other Entities

Kaposi’s sarcoma is a neoplasm that affects both human-immunodeficiency virus (HIV) and non-HIV affected

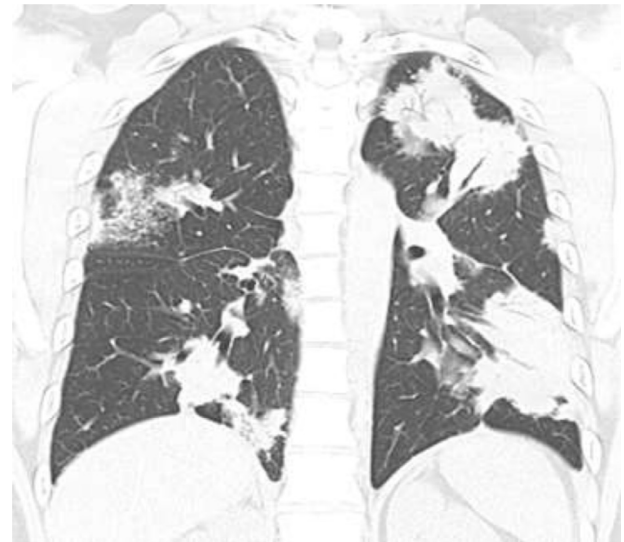


Figure 10 Sarcoid. 35-year-old male with left back pain and fever had a CT demonstrating peribronchovascular soft-tissue mass-like opacities. The patient had confirmed sarcoid on wedge resection. The CT imaging appearance represents the “alveolar” form of sarcoid, which are related to confluent interstitial granulomas. Peripheral nodularity in the right upper lobe can be an indicator of an interstitial process that becomes coalescent.

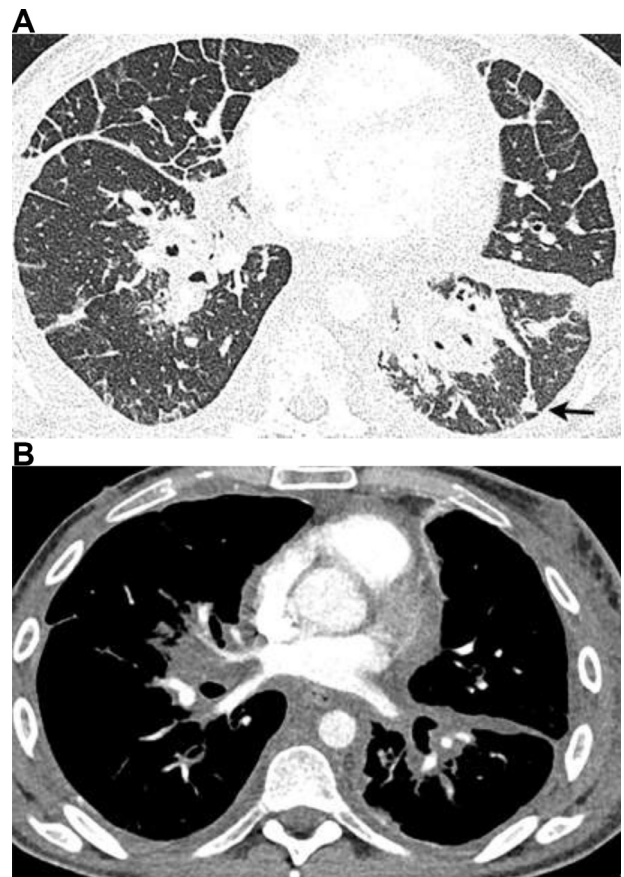


Figure 11 Kaposi’s sarcoma that was related to AIDS. Patient with skin lesions and (A) peribronchovascular soft tissue opacities in the lower lobes with a nodular opacity (arrow) in the left lower lobe are seen. Interlobular septal thickening present particularly in the lingula and right middle lobe. (B) Soft tissue image shows confluent hilar soft tissue representing adenopathy and bilateral pleural effusions.

Table 1 Clinical and Imaging Features That Can Aid in Differential Diagnosis for Peribronchovascular Abnormalities

| Clinical Feature | Diagnostic Considerations |
|---|---|
| Can be asymptomatic | MALToma Sarcoidosis Organizing pneumonia |
| Affects immunocompromised patients | Kaposi's sarcoma (AIDS) Lymphoma (Sjogren's disease, AIDS) Lymphomatoid granulomatosis (autoimmune disease, AIDS, organ transplantation) Follicular bronchiolitis and LIP (autoimmune disease, AIDS) Opportunistic infections including viral, fungal including airway-invasive aspergillosis |
| Skin involvement | Sarcoidosis Lymphomatoid granulomatosis and lymphoma Kaposi's sarcoma Churg-Strauss vasculitis Granulomatosis with polyangiitis IgG4-related lung disease |
| Hemoptysis | Granulomatosis with polyangiitis Intrasleeve hematoma |
| Eosinophilia | Churg-Strauss vasculitis Chronic eosinophilic pneumonia |
| Tracheal and mainstem bronchi involvement | Granulomatosis with polyangiitis Sarcoidosis |
| Asthma | Churg-Strauss vasculitis Chronic eosinophilic pneumonia |
| Upper airway (nasopharynx/ sinus) | Granulomatosis with polyangiitis Churg-Strauss vasculitis IGG4-related lung disease Lymphomatoid granulomatosis |
| Renal disease | Granulomatosis with polyangiitis IGG4-related lung disease Microscopic polyangiitis |
| Imaging feature | |
| Lymphadenopathy present | Infection (bacterial including tuberculosis, viral) Kaposi's sarcoma Lymphoma (with secondary lung parenchyma involvement) Sarcoidosis |
| Less common to have pleural effusions | Organizing pneumonia MALT lymphoma Chronic eosinophilic pneumonia |
| Can be solitary | Lung adenocarcinoma MALT lymphoma (more often multiple) |

individuals. Kaposi's sarcoma is categorized as classical, endemic or African, iatrogenic related to organ transplantation, and AIDS-associated or epidemic, or nonepidemic.⁸⁶ The human herpes virus 8 (HHV-8) causes Kaposi's sarcoma and is termed the Kaposi's sarcoma-associated herpesvirus. HHV-8 is also associated with multicentric Castleman's disease and pleural effusion lymphoma. The prevalence of HHV-8 infection is very high in sub-Saharan Africa and the Mediterranean region, affecting approximately 50% and 10%-30%, respectively.⁸⁷ The virus is believed to activate cellular oncogenes.⁸⁸

Skin lesions, disseminated or localized, are present regardless of the type of Kaposi's sarcoma, and the oral cavity is

affected also. Visceral organ involvement, including the gastrointestinal tract and lungs, is particularly more aggressive in the endemic and AIDS-related forms, while the classic and nonepidemic form tends to be more indolent.⁸⁶ The classic form presents in Eastern European and South American older men, who have occasional visceral organ involvement and adenopathy. The endemic form occurs in younger patients, such as between 25 and 40 years and in children.⁸⁶ The nonepidemic form has been more frequently described in younger men and limited to the skin.⁸⁶

Pathological diagnosis is made by the presence of spindle cells forming vascular spaces around a vessel and proliferation of spindle cells. Staining for latency-associated nuclear

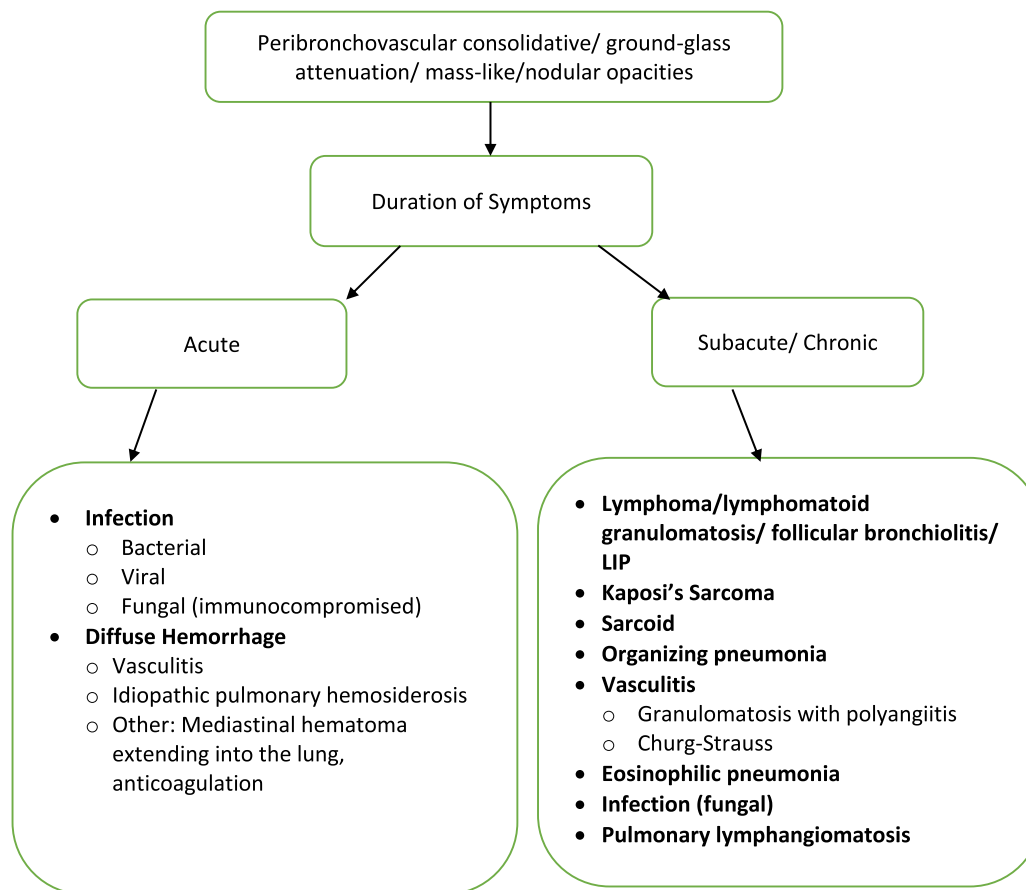


Figure 12 Approach to peribronchovascular CT opacities.

antigen expressed in HHV-8 infected cells and PCR identification of the HHV-8 genome are also methods.⁸⁷

Thoracic involvement in Kaposi's sarcoma has been primarily described in the AIDS-related Kaposi's sarcoma. Kaposi's sarcoma presents as peribronchovascular nodules, pleural effusion, lymphadenopathy, and interlobular septal thickening on chest radiography (Fig. 11). Radiographic findings have been graded as isolated peribronchial cuffing (stage 1); small nodules (stage 2); and large nodules or areas of consolidation (stage 3). Nodules and less commonly masses are frequent, on the order of 90% being bronchovascular and perihilar in distribution. Pleural effusions are described on CT.⁸⁹⁻⁹² Naidich et al. report bilateral pleural effusions in 47% and unilateral effusions in 13% of patients on chest radiograph, and on CT 44% had bilateral pleural effusions, with none unilateral.⁹¹ The lung parenchymal lesions are described as flame-shaped on CT.⁹³ Lymphadenopathy is described in approximately 44%-53% on CT and tends not to be bulky.^{91,93} Imaging with positron emission technology CT reports high-metabolic activity to lesions in the lung and adenopathy, although HIV lymphadenopathy can have abnormal fluorodeoxyglucose uptake.⁹⁴ Lytic bone lesions, skin lesions, and chest wall involvement also can be identified on CT.⁹³ Cardiac involvement also occurs more with immunocompromised AIDS-related cases.^{95,96} Immune reconstitution has been described with Kaposi's sarcoma, when AIDS patients who

are newly placed on antiretroviral therapy have a flare in Kaposi's sarcoma findings.⁹⁷

Pulmonary lymphangiomatosis is a rare entity, described to have smooth peribronchovascular thickening, nodules, ground glass, interlobular septal thickening, and consolidation can occur.⁹⁸ The disease affects mainly young adult and pediatric populations. On pathology, lymphatic proliferation is greater than normal, occurring in areas where lymphatics are typically seen. Lymphangectasia, on the other hand, pathologically entails dilated lymphatic spaces due to lymphatic obstruction.

Diagnostic Approach

The integration of imaging and clinical findings is essential for organizing the differential diagnosis and patient diagnosis. When peribronchovascular findings are identified on CT, specific clinical information can aid in narrowing the differential diagnosis (Table 1). A majority of the diseases tend to occur in patients who are younger than 60-70 years of age, although patients who are older can be affected, such as those with infection, organizing pneumonia, eosinophilic pneumonia, and lymphoma. Infection is a major consideration for acute presentations of patients with peribronchovascular-predominant findings (Fig. 12), and in this scenario, workup for infection would ensue with microbiology, hematology, and assays to identify a causative agent. In

those patients with hemoptysis, vasculitis and a mediastinal source are considerations.

Conclusion

Identifying a peribronchovascular pattern of consolidative and mass-like opacities is useful for developing a differential diagnosis. The peribronchovascular pattern derives from the lymphatics, airways, and pulmonary arteries in this region.

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