Respiratory system involvement in systemic vasculitides

P. Manganelli¹, P. Fietta¹, M. Carotti², A. Pesci³, F. Salaffi¹

ABSTRACT
The respiratory system may be involved in all systemic vasculitides (SV), although with a variable frequency. Lung disease is a very common and important feature of the antineutrophil cytoplasmic antibodies (ANCA)-associated SV (AASV), such as Wegener’s granulomatosis (WG), Churg-Strauss syndrome (CSS), and microscopic polyangiitis (MPA). In WG, almost all patients have either upper airway or lower respiratory tract disease. SOLitary or multiple nodules and masses are the most common findings on chest radiograph. Asthma is a cardinal symptom of CSS, often preceded by allergic rhinitis, frequently complicated by nasal polyposis and sinusitis. Pulmonary transient and patchy alveolar infiltrates are the most common radiographic findings. In MPA, diffuse alveolar hemorrhage (DAH) due to alveolar capillaritis is the most frequent manifestation of the respiratory involvement, clinically expressing with hemoptysis, respiratory distress and anemia. However, DAH may be subclinical and has to be suspected when chest radiograph demonstrates new unexplained bilateral alveolar infiltrates, in the face of falling hemoglobin levels. In giant cell arteritis, the most frequent respiratory symptom is cough, usually nonproductive, persistent, and responsive to corticosteroids. In Takayasu arteritis, pulmonary involvement is frequently subclinical and detectable by noninvasive techniques. Pulmonary involvement is rare in polyarteritis nodosa, Kawasaki disease, Henoch-Schönlein purpura and cryoglobulinemic vasculitis. In conclusion, the involvement of the respiratory system is a very common and important feature of AASV, whereas is less frequent in other SV. It comprises a wide spectrum of clinical features and radiological findings, and may have a prognostic significance. The assessment of the respiratory system should be included in the work-up of all patients with SV, especially of those with AASV.

Introduction
The systemic vasculitides (SV) are a heterogeneous group of rare affections, characterized by a primary process of inflammation and damage of the vessel wall, resulting in blood flow impairment and, ultimately, in ischemia of the supplied tissues (1, 2). The discovery of the antineutrophil cytoplasmic antibodies (ANCA) allowed greater advances in the diagnosis and monitoring of patients with some SV (3, 4). Wegener’s granulomatosis (WG), Churg-Strauss syndrome (CSS) and microscopic polyangiitis (MPA) constitute a subset of small vessel SV usually associated with the presence of ANCA in the serum (5). SV can affect virtually one or more organs and/or systems owing to the size and site of the involved vessels, resulting in a wide variety of signs and symptoms. The respiratory system may be involved in all SV, although more frequently in the ANCA-associated SV (AASV), and rarely in others (i.e. polyarteritis nodosa). In this paper, we review the clinical features, as well as the radiological and pathological findings of the respiratory system involvement in SV, listed according to the Chapel Hill Consensus Conference nomenclature (6) (Table I). Diagnoses of SV were verified by the use of the American College of Rheumatology (ACR) classification criteria (7).

LARGE VESSEL VASCULITIDES
The large vessel vasculitides include giant cell arteritis (GCA) and Takayasu arteritis (TA) (Table I).

Giant cell arteritis
GCA is a granulomatous vasculitis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. GCA mainly
affects white people older than 50 years and is often associated with polymyalgia rheumatica (PMR) (6).

Clinical features and radiological findings

Involvement of the respiratory system has been reported with a frequency ranging from 9% (8) to 31% (9) of GCA patients. The most common respiratory symptom is cough, usually non-productive, persistent, often associated with fever (8, 10-16); it may be the initial manifestation of the disease (12, 14, 15). The cause of cough is unknown, but its prompt remission with corticosteroid therapy suggests a strict causal relationship with GCA (8, 10, 12-16). Less common respiratory symptoms are sore throat, hoarseness, choking sensation, and thoracic pain (8). Pleural effusion is a rare manifestation of the respiratory system involvement in GCA (8, 12, 17-21), also as a presenting form of the disease (19, 20). Interstitial lung disease (ILD) has been reported in GCA patients (22, 23). Basal interstitial fibrosis on chest X-ray has been detected in 16% of a series of 217 patients (24). In single cases, interstitial infiltrates or pulmonary nodules may be related to another concomitant SV, such as CSS (25,26) or WG (27). Intra-alveolar haemorrhage favourably responsive to prednisone therapy has been recently reported in a case of GCA (28). In GCA patients, chest radiograph may show aneurysm of the thoracic aorta, even many years after cranial symptoms have subsided (29). Such a complication of GCA may also be an occasional radiological finding, or discovered in consequence of the appearance of a new aortic insufficiency murmur (29). The early diagnosis of thoracic aortic aneurysm and its surgical treatment are very important, since mortality is markedly increased in GCA complicated by thoracic aortic dissection (30).

Pathological findings

GCA can affect the main pulmonary arteries, as well as large and medium-sized pulmonary elastic arteries (31). The vasculitic process is characterized by medial and adventitial chronic inflammation with giant cells and causes elastic laminae destruction, sometimes associated with focal fibrinoid necrosis in the media (31). Transbronchial or open lung biopsies may show bronchial, vascular, interstitial or peribronchial ill-defined granulomas (11,22). Bronchoalveolar lavage (BAL), performed in three GCA patients with respiratory symptoms and normal chest radiograph, demonstrated a T-lymphocyte alveolitis with CD4+ cell predominance (32).

Takayasu arteritis

TA is an uncommon granulomatous vasculitis that mainly involves the aorta and its major branches and usually affects women under 50 years of age (6).

Clinical features and radiological findings

Pulmonary disease in TA usually presents as cough, dyspnea, and/or hemoptysis. Sometimes exertional dyspnea due to pulmonary artery involvement may be the initial clinical symptom of TA (33). The reported incidence of the pulmonary artery involvement by angiography ranges widely, from 14% to 100%, with an average of 56% in nine series totalling more than 250 cases (34). Rarely the pulmonary artery involvement may be isolated with clinical features similar to those of thromboembolic lung disease (34-37). The diagnosis can be derived from angiographic findings, showing pulmonary artery stenosis or occlusion of one of its branches (38). However, this technique is not able to differentiate active inflammation from vascular damage caused by “burnt-out” TA. Thus, cross-sectional imaging techniques, such as computed tomography (CT) angiography (39) and magnetic resonance (MR) (40), are useful in detecting mural changes in the pulmonary artery. MR angiography (MRA) is steadily replacing conventional contrast angiography for obtaining a generalized arterial survey in TA (41). In a study with MRA, it has been shown that all of 10 pulmonary artery lesions found on conventional angiography were also demonstrated on MRA (42). It is noteworthy that pulmonary vascular involvement in TA is frequently subclinical and detectable by non-invasive techniques. Indeed, Umehara et al. (43) retrospectively evaluated 180 perfusion lung scans of 120 Japanese patients with TA, showing abnormal lung scans in the majority (76%). The data obtained by spirometry and arterial blood gas analysis were weakly correlated with the severity of perfusion lung scan findings (41). Vanoli et al. (44) carried out a prospective analysis of pulmonary involvement in 15 Italian patients free of respiratory symptoms, by means of chest X-ray, spirometry, planar and tomographic single-photon emission tomography (SPET) perfusion/ ventilation lung scintigraphy, and color-doppler echocardiography. In all patients standard chest X-ray and ventilation scintigraphy were normal, whereas 9/15 (60%) patients showed unmatched segmental perfusion defects (41 by planar evaluation vs 48 by SPET). Thirteen patients underwent spirometry, which proved to be abnormal in 5 (38%). No patient had pulmonary hypertension attributable to TA on color-doppler echocardiography (44). Other manifestations of the respiratory system involvement in TA include pleural effusion (5% of cases) (44), rarely bilateral (46), recurrent pulmonary artery hemorrhage leading to severe respiratory failure (47), and pulmonary infil- trates (46). On chest X-ray, basal interstitial fibrosis has been reported in 3% of a series of 63 TA patients (24). In single cases, parenchymal consolidations due to pulmonary hemorrhage...
or to an organized thrombus with prominent endovascular recanalisation, associated with a granulomatous process within the pulmonary arterial wall (49), may be other manifestations of lung disease in TA.

**Pathological findings**

The histopathological findings of the pulmonary artery are very similar to those of the aorta and its branches (50). The adventitia, media, and intima are infiltrated by mononuclear and giant cells, forming necrotizing or non-necrotizing granulomas. The fragmentation of elastic fibres (elasticophagia) is a prominent finding, and the destruction of the smooth muscle cells in the media leads to weakening of the vessel wall and lumen dilatation. Later, diffuse or nodular fibrosis may predominate and result in stenosis or obliteration of the vascular lumen (51). Both inflammatory and fibrotic stages may co-exist. Stenosis and occlusions are common, as well as stenosis-recanalization lesions of the pulmonary elastic arteries (50). The histopathological findings of the isolated pulmonary TA are distinctive and differ in many aspects from those of systemic arteritis (52). In single cases, the pathological findings of pulmonary parenchyma were consistent with acute interstitial pneumonia (53) or usual interstitial pneumonia (54).

**MEDIUM-SIZED VESSEL VASCULITIDES**

Medium-sized vessel vasculitides refer to “classical” polyarteritis nodosa (PAN) and Kawasaki disease (KD) (6) (Table I).

**Polyarteritis nodosa**

PAN is a necrotizing vasculitis of medium-sized arteries without glomerulonephritis, or vasculitis in arterioles, capillaries, or venules (6).

**Clinical features**

The respiratory system involvement in PAN is very rare (55). Early series of PAN indicated pulmonary disease in up to 47% of patients (56), but it has been determined that these cases actually are more consistent with MPA or CSS. Recently, a case of classical PAN was found to have diffuse interstitial and alveolar infiltrates on chest X-ray and bilateral diffuse patchy areas of consolidation on high-resolution computed tomography (HRCT) (57). Thoracoscopic lung biopsy revealed a necrotizing arteritis of medium-sized muscular pulmonary arteries. The treatment with prednisone and cyclophosphamide was successful (57). Guo et al. (58) described a patient with hepatitis B virus (HBV)-related PAN complicated by diffuse alveolar hemorrhage (DAH), who died of respiratory failure. The cause of DAH in this patient was unclear, but a role for recurrent attacks of malignant hypertension has been suggested (56). Menon et al. (59) described another case of HBV-related PAN and DAH in which the treatment with corticosteroids and plasmapheresis obtained the clearing of the infiltrates on chest radiograph.

**Pathological findings**

A detailed pathologic analysis of pulmonary involvement in PAN has been reported by Matsumoto et al. (60) in ten cases on autopsy. Arteritis affecting bronchial arteries was present in seven, diffuse alveolar damage (DAD) involving all lobes bilaterally in five, acute in two and organizing in three, and interstitial fibrosis with honeycomb lung in another two. Five patients died of respiratory failure resulting from DAD.

**Kawasaki disease**

KD is a vasculitis usually occurring in children, involving large, medium-sized and small arteries, and associated...
with mucocutaneous lymph node syndrome. Coronary arteries are often involved; aorta and veins may also be affected by the disease (6).

Clinical features and radiological findings
The prevalence of the respiratory system involvement in KD likely depends on the ethnic origin of patients. As a matter of fact, in a series of 129 Japanese patients, abnormal chest X-ray findings were found in 14.7% (61). A reticulo-micronodular pattern was the more frequent abnormality (89.5%), followed by peribronchial cuffing (21.1%), pleural effusion (15.8%), atelectasis (10.5%), and air trapping (5.3%). All these radiological abnormalities appeared within 10 days after the disease onset. On the other hand, in a multicenter, retrospective study of 250 Italian patients with KD, pulmonary involvement has not been described (62). ILD and pleural effusions in a 6-year-old girl (63), as well as persistent lobar lung consolidation unresponsive to antibiotic therapy as the main manifestations of atypical KD in two young children (64), have been recently reported.

Pathological findings
The information on the lung pathology in KD is scanty. Chronic interstitial pneumonitis, with focal organizing pneumonia and fibronous pleuritis without evidence of vasculitis, have been described in a lung biopsy specimen (65). Parenchymal nodules with predominantly mononuclear cell infiltrates within the lung parenchyma and the vessel walls, as well as IgA plasma cells (PCs) in the nodules, have been recently reported in three KD patients (65). In a study, IgA PCs were significantly increased in the trachea of 18 KD patients compared with that of 10 controls, predominantly located around submucosal glands, including those of larger bronchi (66). It has been suggested that the upper respiratory tract may be the portal entry of the still unidentified KD etiologic agent, resulting in a local IgA immune response that may play an important pathogenetic role (66).

Small vessel vasculitides
Small vessel vasculitides include WG, CSS, MPA, Henoch-Schönlein purpura (HSP), essential cryoglobulinemic vasculitis (CV), and cutaneous leukocytoclastic angiitis (6) (Table I). Cutaneous leukocytoclastic angiitis is not included in this review, owing to the absence of lung involvement.

Wegener’s granulomatosis
WG is a disease characterized by granulomatous inflammation of the ear-nose-throat area with necrotizing vasculitis affecting small to medium-sized vessels (capillaries, venules, arterioles, and arteries). Necrotizing glomerulonephritis is common (6).

Clinical features
The respiratory tract is frequently involved, since almost all WG patients have either upper airway or pulmonary disease (67, 68). Clinical manifestations of upper respiratory tract involvement include nasal obstruction due to mucosal swelling, bloody or purulent nasal discharge, sinus pain, oral/and or nasal ulcers, tick crusts, and nasal septal perforation with saddle nose deformity (67, 68). Clinical manifestations related to lower respiratory tract disease include cough, dyspnea, and hemoptysis. WG patients may also suffer from pleuritic pain. Tracheo-bronchial involvement is a significant cause of morbidity and may be found in WG patients presenting with hemoptysis, dyspnea on exertion, stridor or wheezing (69). However, it may also be an unsuspected finding in those who undergo bronchoscopy primarily because of parenchymal abnormalities on chest-X ray (69). Tracheo-bronchial disease includes subglottic stenosis, ulcerating tracheo-bronchitis, and cica-tricial tracheal or bronchial stenoses without signs of active inflammation at bronchoscopy (69). Subglottic tracheal stenosis is reported in up to 23% of patients, being the presenting feature of the disease in 2.6% (70). It may also occur in up to 49% of patients in the absence of other features of active WG (70). Dyspnea, hoarseness, voice changes, and stridor are the most frequent symptoms. Subglottic stenosis may be a potentially life-threatening complication of WG, requiring emergency tracheostomy (69), manual or laser dilatation (68), laryngotracheoplasty (70), and intratracheal dilatation with local corticosteroid injection (70). Pleural effusion, usually small, unilateral and non-hemorrhagic, is not rare, being reported in up to 12.4% of patients (71). DAH due to alveolar capillaritis is increasingly recognized as a prominent pulmonary manifestation of WG, reported in 5-45% of cases (72). Patients with DAH present with cough, dyspnea, hemoptysis and anemia.

Radiological findings
Almost all patients with WG have an abnormal chest radiograph. Single or multiple nodules with either well-circumscribed or ill-defined margins, and masses are the most common radiological findings (77-79). The nodules are diffuse in distribution, and approximately one-half are cavitated (80, 81). Diffuse alveolar opacities due to DAH, atelectasis and/or obstructive pneumonia caused by bronchial stenosis, uni
or bilateral infiltrates, nodular or linear opacities, and pleural effusion may be other findings on chest X-ray. CT and HRCT may demonstrate nodules and cavitation not apparent in radiographs. CT and HRCT may also show blood vessels heading to nodules and cavities (“feeding vessels”), irregular and stellate-shaped peripheral pulmonary arteries larger than the corresponding bronchi (“vasculitis sign”), small peripheral wedge-shaped consolidation abutting the pleura and simulating pulmonary infarction, and cuffing of the bronchovascular bundle distributed mainly around lobar, segmental, and subsegmental bronchi (78, 79, 82). Pulmonary nodules may be surrounded by a rim of ground-glass opacity (“halo sign”) (79, 83). Other CT and HRCT findings include consolidation, patchy or diffuse ground-glass opacities (Figs. 3, 4), or both. Additional CT and HRCT findings include stenoses of the larynx or tracheo-bronchial tree, bronchial wall thickening in the segmental or subsegmental bronchi, bronchiectasis, lobar or segmental atelectasis, parenchymal bands, interlobular septal thickening, septal and non-septal lines, nodular pleural thickening, pleural effusion, hilar and/or mediastinal lymphadenopathies (77, 78, 83-87). HRCT may also differentiate the active from inactive disease after immunosuppressive therapy. Ground-glass opacities, cavitating nodules/masses (Fig. 5) and masses measuring more than 3 cm represent active disease (87). Non-cavitary small nodules and sepsal or non-septal lines can be either active or cicatricial lesions (87). Parenchymal (84, 87) and airway lesions (84) may improve with treatment in most patients. However, treated pulmonary WG leaves substantial residual damage, since in a recent study with HRCT only 12 of 28 (43%) patients were free from lesions after remission-inducing treatment (87).

Pathological findings
The main pathological lung findings include parenchymal necrosis, vasculitis, and granulomatous inflammation, characterized by an infiltrate composed of a mixture of neutrophils, lymphocytes, plasma cells, histiocytes, and eosinophils (88). Parenchymal necrosis can take the form of either neutrophilic microabscesses (“dirty” appearance) or areas of geographic necrosis, with a basophilic, granular center often surrounded by a peripheral rim of palisading histiocytes and multinucleated giant cells. Vasculitis may affect arteries, veins, and capillaries. The main histopathologic features of pulmonary capillaritis include capillary wall necrosis with infiltration by neutrophils, intra-alveolar and frequently interstitial red blood cells, hemosiderin deposition within alveolar macrophages and in the interstitium, as well as fibrin thrombi occluding capillaries in the interalveolar septa. Immunohistology and electron microscopy rarely demonstrate immune deposits (“pauci-immune” capillaritis). Many of the neutrophils undergo fragmentation and eventually become pyknotic, findings which support a pathogenetic role for neutrophil by-products such as oxygen radicals and proteolytic enzymes in this form of lung injury. WG can also involve the airways and cause a variety of bronchial/bronchiolar lesions, such as acute and chronic bronchiolitis, follicular bronchiolitis, bronchiolitis obliterans, non-necrotizing and necrotizing granulomatous inflammation, and bronchial stenosis (88, 89). Pleural changes, such as acute
fibrinous pleuritis and chronic and/or fibrous pleuritis, may also be present (88, 89). In patients with active disease, BAL demonstrates the presence of alveolitis characterized by roof ridge of all neutrophils, followed by lymphocytes, and eosinophils, as well as phagocytosis of neutrophils and their remnants by alveolar macrophages (90, 91). The BAL cell profile depends on the underlying lesion (91). Indeed, in highly active disease associated with diffuse infiltrates on chest radiograph, the BAL cell profile is dominated by neutrophils (91). In lung disease of low or moderate activity, radiologically characterized by nodular or linear opacities, lymphocytes predominate, with prevalence of CD4+ T cells and Th1 cytokine profile (91, 93). In patients with subclinical alveolar hemorrhage, BAL may show the presence of siderophages in a percentage of more than 5% correlating with disease activity (94).

**Churg-Strauss syndrome**

CSS is a rare multisystemic disorder characterized by eosinophil-rich and granulomatous inflammation involving the respiratory tract, and necrotizing vasculitis affecting small to medium-sized vessels, associated with asthma and eosinophilia (6).

**Clinical features**

The clinical picture of CSS consists of three partially overlapping phases (95). The prodromal phase is dominated by the allergic disease, consisting of asthma, often preceded by allergic rhinitis that is frequently complicated by nasal polyposis and sinusitis. The second phase is characterized by peripheral blood eosinophilia and eosinophilic infiltrative disease. Manifestations of systemic vasculitis generally occur in the third phase of CSS (95). Asthma is a cardinal symptom, occurring in more than 95% of patients, and an important ACR classificative criterion of CSS owing to its high sensibility (100%) and specificity (96.3%) (96). Asthma usually precedes vasculitis for an average of 3 to 8 years (97), and up to 61 years (98). A relatively short interval from onset of asthma to appearance of vasculitis is an unfavourable prognostic sign (99, 100). Asthma may remit once vasculitis develops, but often reappears as a major clinical problem in the post-vasculitic phase of the disease (95). The severity of asthma may require long-term oral corticosteroid therapy for adequate control. Prolonged treatment with oral steroids may suppress or delay the development of overt CSS that, therefore, becomes evident with tapering or discontinuation of corticosteroid therapy, as occurs after the introduction of anti-asthmatic drugs such as leukotriene receptor antagonists (101-103), or the switch to inhaled steroids (104, 105). Other less common manifestations of the respiratory system involvement in CSS include DAH (106-109), and exudative pleuritis (95, 98, 106, 110-112).

**Radiological findings**

Pulmonary transient and patchy alveolar infiltrates, without a lobar or segmental distribution, represent the most frequent radiological findings (95, 100, 106, 108, 112). Chest radiograph may also demonstrate pulmonary nodules that rarely cavitate, diffuse reticulo-nodular opacities, bronchial wall thickening, hilar lymph node enlargement, and pleural effusion (95, 98, 112, 113). In a cohort of 17 CSS patients evaluated by CT (3 patients) and HRCT (14 patients), the most common abnormality consisted of parenchymal opacification (consolidation or ground-glass attenuation), predominantly peripheral or random in distribution (114). Choi et al (113) evaluated 9 CSS patients by HRCT, showing bilateral patchy ground-glass opacity and airsacpace consolidation with predominantly subpleural distribution, in some patients surrounded by the ground-glass opacity (“halo sign”) (Fig. 6), and diffusely scattered centrilobular nodules with a diameter less than 5 mm, more prominently distributed within the lesion of ground-glass opacity (Fig. 7).

**Pathological findings**

The major histopathologic findings in the lung include a combination of extravascular granulomas, vasculitis, and eosinophilic pneumonia (115). These findings may occur isolatedly or co-exist (95). Granulomas are composed by a central, eosinophilic core surrounded by radially arranged epithelioid histiocytes and giant cells (116). Vasculitis is characterized by intimal and medial infiltration by chronic inflammation containing numerous eosinophils (115). Eosinophilic pneumonia is characterized by the accumulation within alveolar spaces of an eosinophil and macrophage-rich infil-
trate that may induce alveolar septal expansion (115). Pleural effusion is not a rare manifestation of CSS (95, 106, 109), characterized by an exudate rich of eosinophils (95, 106, 110, 112). Pleural biopsy may show pleural thickening, eosinophilic infiltration, and necrotizing granulomas (111). Eosinophilia, ranging from 4% to 66%, is the most common abnormality in the BAL cell profile (100, 117-120). BAL eosinophilia is more sensitive in reflecting disease activity than the eosinophil count in the blood (119). In CSS patients with subclinical alveolar hemorrhage, BAL may show the presence of siderophages in a percentage of more than 5% correlating with disease activity (104).

Microscopic polyangitis

MPA is a necrotizing vasculitis, with few or no immune deposits, affecting small vessels (capillaries, venules, or arterioles). Necrotizing arteritis involving small and medium-sized arteries may also be present. Necrotizing glomerulonephritis is very common, and pulmonary capillaritis often occurs (6).

Clinical features

DAH due to alveolar capillaritis is the most frequent manifestation of lung involvement in MPA, occurring in up to 29% of patients (121). DAH is also an important contributory factor for morbidity and mortality in this disease (72, 122). Chronic persistent or recurrent DAH may cause obstructive lung disease, with the physiological and CT appearance of emphysema (123, 124) and pulmonary fibrosis (124). Pleurisy with or without effusion is less frequent (121). Pulmonary interstitial fibrosis may be an early manifestation of the disease, antedating the diagnosis of MPA by two or more years (125, 126), and is associated with a poor prognosis (126).

Pathological findings

In MPA the most common pathological lung findings are neutrophilic capillaritis and acute or chronic alveolar hemorrhage (89). Other pathological findings are bronchiolitis obliterans organizing pneumonia (BOOP), interstitial fibrosis, acute and chronic DAD, and fibrous pleuritis (89).

Henoch-Schönlein purpura

HSP is a vasculitis with IgA-dominant immune deposits, affecting small vessels with predominant cutaneous, intestinal, renal, and articular involvement (6). HSP preferentially affects children between the ages of 5 and 15 years, more commonly boys than girls (127). HSP is less frequent but more severe in adults (127).

Clinical features

Clinically important involvement of the respiratory system is uncommon in HSP. In both young (128-134) and adult (135, 136) patients, the more severe lung manifestation is pulmonary hemorrhage that may have a fatal outcome (128, 130, 131). Usual interstitial pneumonia has been recently reported in a patient with adult HSP (136). PFTs have been carried out in two series of children with HSP. Chaussain et al (137) evaluated 29 patients free of pulmonary symptoms and reported a decreased DLCO in 28 (96%). In 19 patients, DLCO measurements were performed at 3-month intervals during the follow-
Main lung pathologic findings
Vasculitis of pulmonary arteries with giant cells, granulomatous necrotizing or non-necrotizing vasculitis

Clinical features and radiological findings
In mixed cryoglobulinemia (MC), clinical involvement of the respiratory system is usually mild to moderate. Patients may present cough, dyspnea on exertion, asthma, and pleurisy (142-144). Severe lung involvement, due to alveolar hemorrhage (145, 146), adult respiratory distress syndrome (147), or acute lung injury (148), is very rare, being reported only in anecdotal cases. Chest X-ray and HRCT may show interstitial lung fibrosis (142-144).

Discussion
The involvement of the respiratory system is a very common and important feature of AASV, while it is less frequent in other SV. It includes a wide spectrum of clinical features and radiological findings and may condition the outcome of SV patients. Table II and Table III summarize the distinguishing features of pulmonary involvement in large and small vasculitides, respectively. At present, it is unclear the reason of the different frequency of the respiratory system disease in SV, as well as the peculiar involvement of the bronchial rather than pulmonary arteries in PAN. CT and HRCT have a higher sensitivity than chest radiograph in demonstrating airway, parenchymal, and pleural lesions. However, many of these studies suggest an early and transient subclinical lung impairment in children with HSP during the active phase of the illness. It has been suggested that the impairment of DLCO may be due to alteration of the alveolar capillary membrane related to IgA deposition during the active phase of HSP vasculitis (137). In adults, HSP may represent a clinical manifestation of lung cancer (139-141).

Pathological findings
Pathological study performed in a few cases demonstrated necrosis of capillary walls with septal and intra-alveolar hemorrhage (128, 129). In a case immunohistochemical analysis showed extensive granular deposition of IgA along the alveolar septa adjacent to areas of hemorrhage, suggesting an immune-pathogenetic mechanism in the development of pulmonary lesions (128).

Cryoglobulinemic vasculitis
CV is a small vessel vasculitis associated with cryoglobulins in serum; skin and glomeruli are often involved (6).

Table II. Distinguishing features of pulmonary involvement in large vessel vasculitides

<table>
<thead>
<tr>
<th></th>
<th>GCA</th>
<th>TA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary arteries involvement</td>
<td>Rare</td>
<td>Common</td>
</tr>
<tr>
<td>Lung parenchyma involvement</td>
<td>Rare</td>
<td>Normal</td>
</tr>
<tr>
<td>Respiratory symptoms</td>
<td>Non-productive cough (most common), sore throat, hoarseness, coughing sensation, thoracic pain</td>
<td>Cough, dyspnea, hemoptysis</td>
</tr>
<tr>
<td>Radiological findings</td>
<td>Basal interstitial fibrosis, pleural effusion, interstitial infiltrates/nodules (due to concomitant SV), aneurysm of the thoracic aorta (usually later finding)</td>
<td>Stenosis or occlusion of pulmonary artery, basal interstitial fibrosis, pleural effusion, pulmonary infiltrates, peripheral defects at lung scintigraphy</td>
</tr>
<tr>
<td>Main lung pathologic findings</td>
<td>Vasculitis of pulmonary arteries with giant cells, interstitial, bronchial and peribronchial granulomas</td>
<td>Granulomatous necrotizing or non-necrotizing vasculitis of pulmonary arteries, diffuse or nodular fibrosis of vessel wall resulting in stenosis or obliteration of vascular lumen</td>
</tr>
</tbody>
</table>

Prominent BAL findings
H-lymphocyte alveolitis
Unknown

GCA: Giant cell arteritis; TA: Takayasu arteritis; BAL: bronchoalveolar lavage; SV: systemic vasculitides.
Table III. Distinguishing features of pulmonary involvement in small vessel vasculitides.

<table>
<thead>
<tr>
<th>Lung Involvement</th>
<th>WG</th>
<th>CSS</th>
<th>MPA</th>
<th>HSP</th>
<th>CV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most common HRCT findings</td>
<td>Multifocal nodules, often cavitated parenchymal opacification (consolidation and/or ground-glass attenuation)</td>
<td>Parenchymal opacification (consolidation and/or ground-glass attenuation) (DAH)</td>
<td>Ground glass opacities</td>
<td>Diffuse alveolar hemorrhage (DAH)</td>
<td>Capillaritis and DAH</td>
</tr>
<tr>
<td>Bronchopulmonary pathologic findings</td>
<td>Necrotizing granulomatous vasculitis, capillaritis</td>
<td>Extravascular granulomas, vasculitis, eosinophilic pneumonia</td>
<td>Capillaritis and DAH</td>
<td>Capillaritis and DAH</td>
<td>Capillaritis and DAH</td>
</tr>
<tr>
<td>BAL findings</td>
<td>Neutrophilia, red blood cells and eosinophils (&gt;30% of DAH)</td>
<td>Eosinophilia</td>
<td>Red blood cells and leukocytes (&gt;50% of DAH)</td>
<td>-</td>
<td>T lymphocytes</td>
</tr>
</tbody>
</table>


these radiological findings are non-specific and, therefore, their interpretation might be confused with those of other patients with SV, especially those with AAV.

**References**

Respiratory system involvement in systemic vasculitides / P. Manganelli et al.

Respiratory system involvement in systemic vasculitides / P. Manganelli et al.


