Review

Respiratory system involvement in systemic vasculitides

P. Manganelli[1], P. Fietta[1], M. Carotti[2], A. Pesci[3], F. Salaffi[4]

[1]Dipartimento Osteo-Articolare, Unità Operativa di Reumatologia e Medicina Interna, Azienda Ospedaliera-Universitaria di Parma; [2]Istituto di Radiologia, Università Politecnica delle Marche; [3]Dipartimento di Clinica Medica, Nefrologia e Scienze della Prevenzione, Unità Operativa di Pneumologia, Università degli Studi di Parma; [4]Clinica Reumatologica, Università Politecnica delle Marche, Italy.

Paolo Manganelli, MD, Director, Dip. Osteo-Articolare; Pieranna Fietta, MD, Researcher; Marina Carotti MD, Associate Professor; Alberto Pesci, MD, Associate Professor; Fausto Salaffi, MD, PhD, Associate Professor.

Please address correspondence to: Salaffi Fausto, MD, Clinica Reumatologica, Università Politecnica delle Marche, Ospedale A. Murri, Via dei Colli no. 52, 60035 Jesi, Italy.
E-mail address: fsalaff@tin.it

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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 non-productive, persistent, and responsive to corticosteroids. In Takayasu arteritis, pulmonary involvement is frequently subclinical and detectable by non-invasive 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

Table I. Classification of SV according to the Chapel Hill Consensus Conference nomenclature (4).

Large vessel vasculitides
- Giant cell arteritis
- Takayasu arteritis

Medium-sized vessel vasculitides
- Polyarteritis nodosa
- Kawasaki disease

Small vessel vasculitides
- Wegener's granulomatosis
- Churg-Strauss syndrome
- Microscopic polyangiitis
- Henoch-Schönlein purpura
- Cryoglobulinemic vasculitis
- Cutaneous leukocytoclastic angiitis

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 hemorrhage leading to severe respiratory failure (47), and pumonary infiltrates (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

(48) (Figs. 1, 2), 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).

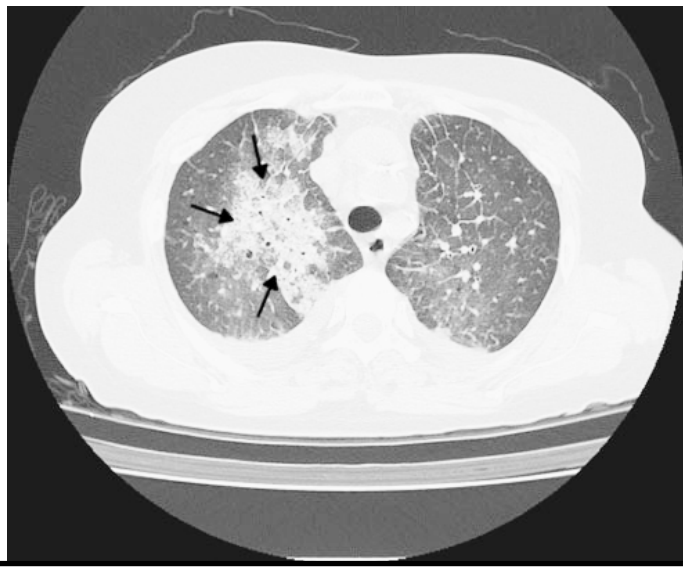

Fig. 1. Takayasu arteritis. CT scan demonstrates heterogeneous consolidation of the right upper lobe due to pulmonary hemorrhage (arrows).

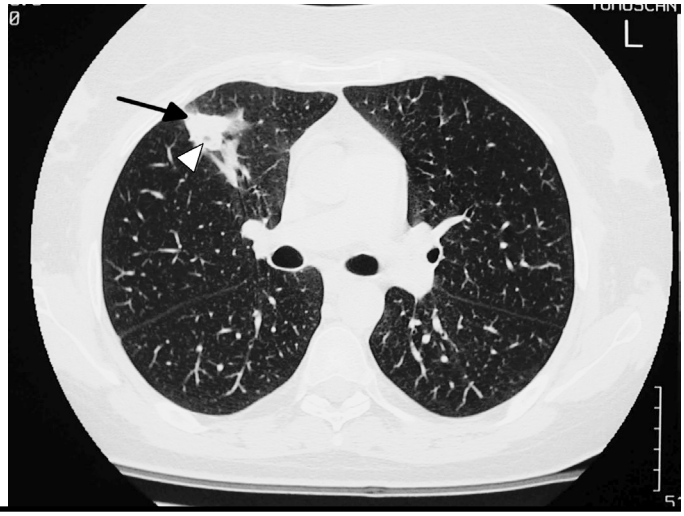

Fig. 2. Takayasu arteritis. CT scan shows a focal consolidation in the anterior segment of the right upper lobe (arrow) with a small area of cavitation (arrowhead).

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 fibrinous 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 cicatricial 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 preminent pulmonary manifestation of WG, reported in 5-45% of cases (72). Patients with DAH present with cough, dyspnea, hemoptysis and anemia. Chest radiograph showing new unexplained bilateral alveolar infiltrates in the face of falling hemoglobin levels must alert physicians about the presence of symptom-free DAH. Increased values of the diffusing capacity for carbon monoxide (DLCO) and the presence of siderophages (iron-laden alveolar macrophags) in BAL allow to the diagnosis of alveolar hemorrhage. The lavage effluent is bloody when hemorrhage is recent. DAH may be the initial manifestation of the disease (73), and lead to acute respiratory failure requiring mechanical ventilation (74). The related mortality is very high (50% of cases) (68, 72, 74). On pulmonary function tests (PFTs) airflow obstruction is the most frequent functional abnormality in WG, often associated with a reduced DLCO; reduction of lung volumes may also occur (75). In patients with subglottic stenosis, the flow-volume curve shows a flattening of both inspiratory and expiratory limbs of the loop, consistent with an extrathoracic airway obstruction (70). Occasionally, large vessel disease such as pulmonary artery stenosis may occur in WG (76).

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, ilar 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 septal 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).

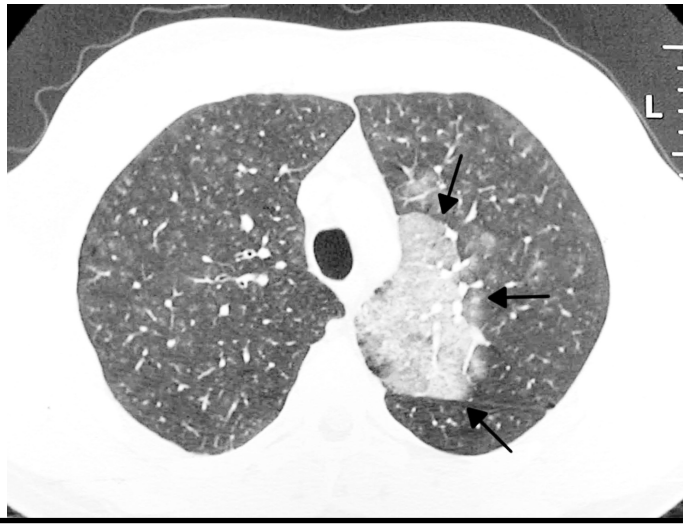

Fig. 3. Wegener's granulomatosis. Thin section CT scan at the upper lobes shows ground-glass opacity in the upper left lobe due to pulmonary hemorrhage (arrows).

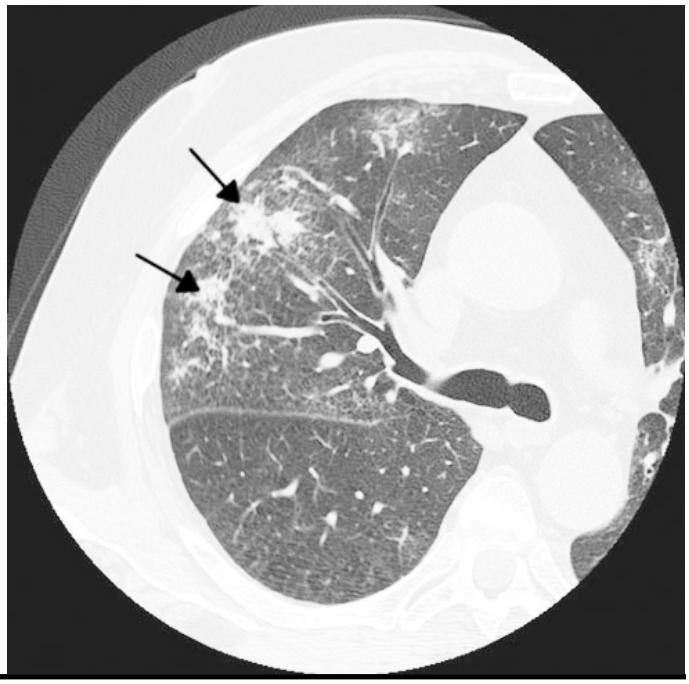

Fig. 4. Wegener's granulomatosis. Thin section CT scan at carina shows multifocal patchy ground-glass opacity around the patchy consolidation showing halo sign in the right middle lobe (arrows).

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 neutrophils 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

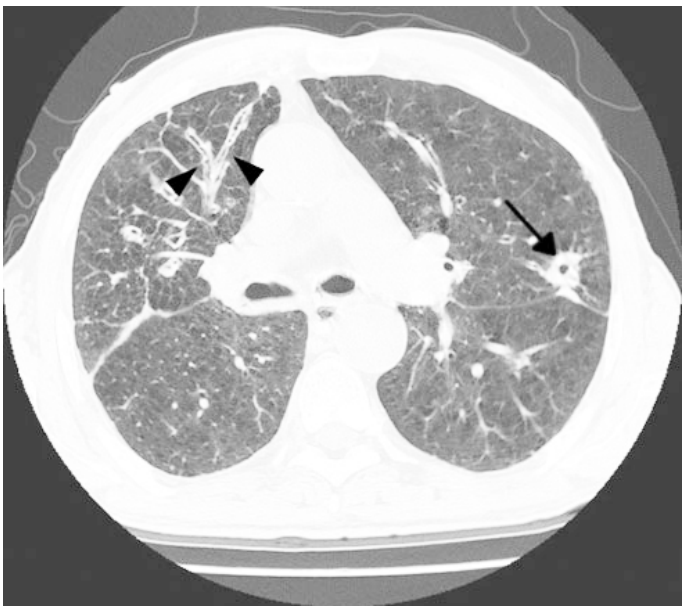

Fig. 5. Wegener's granulomatosis. Thin section CT scan at carina shows cavitating nodule in the lingular division of the left upper lobe (arrow). Bronchial wall thickening is evident in the right middle lobe (head arrows).

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 adeguate 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 reticulonodular 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 airsapace 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 histopatologic 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 polyangiitis

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 fibrinous pleuritis (89).

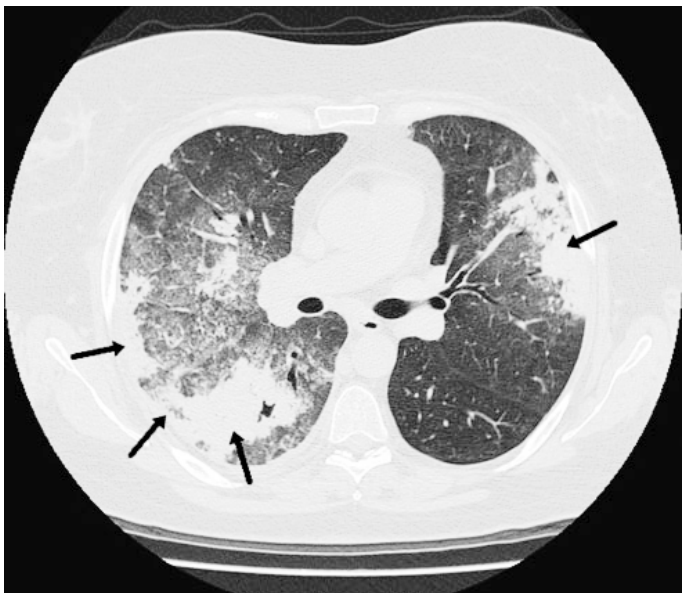

Fig. 6. Churg-Strauss syndrome. Thin section CT scan at carina shows multifocal patchy ground-glass opacity around the patchy consolidation showing halo sign (arrows).

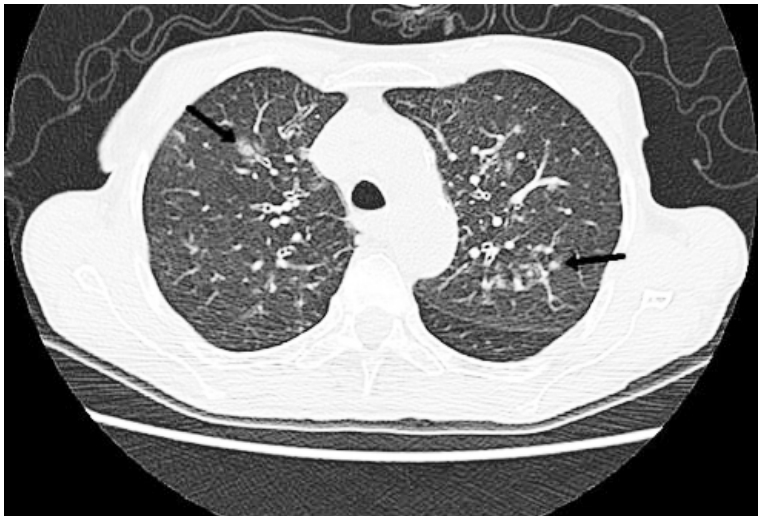

Fig. 7. Churg-Strauss syndrome. CT scan shows small centrilobular nodules at the upper lobes and within the lesion of ground-glass opacity at the left upper lobe (arrows).

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-

up. Normalization of DLCO values was observed in children who completely recovered from HSP, whereas those with persisting symptoms had low DLCO values (134). Cazzato *et al.* (138) performed PFTs in 15 patients without clinical and radiological evidence of lung involvement at the disease onset. After a mean of 21 months, PFTs were repeated in 10 of the previously studied children. During the acute phase of the disease, DLCO was found to be significantly lower in children with HSP than in controls. Overall, the results 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 immunopathogenetic 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).

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 anedoctal cases. Chest X-ray and HRCT may show interstitial lung fibrosis (142-144). Chest radiograph may also demonstrate pulmonary infiltrates (145, 146, 149), cavitary lesion and pleural thickening (149). PFTs may show small airway disease and DLCO reduction (142-144, 150), and 67-Gallium scintigraphy hilar and/or parenchymal uptake of the radionuclide (144).

Pathological findings

The information on the lung pathology in MC is very scanty. Widespread vasculitis involving small and medium vessels in the lung, as well as in other organs, has been reported in postmortem examination of 5 out of 40 patients (151). Diffuse pulmonary vasculitis was also found at autopsy in a patient with MC associated with hepatitis C virus (HCV) who died of respiratory failure (152). In another MC patient open lung biopsy revealed BOOP (149). BAL performed in non-smoking patients with HCV-associated MC, without pulmonary symptoms and with normal chest radiograph, demonstrated a lower percentage of alveolar macrophages and a higher percentage of T CD3+ lymphocytes than healthy controls (150). Thus, BAL results indicated a subclinical T-lymphocyte alveolitis in MC HCV+ patients, not predictive of deterioration in lung function in a 5-year follow-up (150).

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

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

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

Lung Involvement	WG Common	CSS Common	MPA Frequent	HSP Rare	CV Rare
PFTs	Restrictive/Obstructive syndrome, DLCO ↓ or ↑(DAH)	Obstructive pattern	↑ DLCO	↓ DLCO	Obstructive pattern
Most common HRCT findings	Multiple nodules often cavitated	Parenchymal opacification (consolidation and/or ground-glass attenuation)	Parenchymal opacification (consolidation and/or ground-glass attenuation) (DAH)	Ground-glass opacities	Infiltrates, fibrosis
Main lung pathologic findings	Necrotizing granulomatous vasculitis, capillaritis	Extravascular granulomas, vasculitis, eosinophilic pneumonia	Capillaritis and DAH	Capillaritis	Small and medium vessel vasculitis
Prominent BAL findings	Neutrophilia, red blood cells and siderophages (>30%) if DAH	Eosinophilia	red blood cells and siderophages (>30%) if DAH	-	T-lymphocyte alveolitis

DLCO: Diffusing capacity for carbon monoxide; ANCA: Antineutrophil cytoplasmic antibodies; DAH: Diffuse alveolar haemorhage; WG: Wegener's granulomatosis; CSS: Churg-Strauss syndrome; MPA: Microscopic polyangiitis; HSP: Henoch-Schönlein purpura; CV: Cryoglobulinemic vasculitis; HRCT: High-resolution computed tomography.

these radiological findings are non-specific and, therefore, their interpretation must take into account the whole of clinical, laboratory and pathological data. In SV patients presenting pulmonary symptoms during the treatment with immunosuppressive agents, it is imperative to exclude the presence of lung infection. Therefore bronchoscopy with transbronchial biopsy and BAL is often needed to exclude infection or, alternatively, to establish a microbiological diagnosis by performing the appropriate stains and cultures. Moreover iatrogenic pulmonary complications needed to be taken into account in the differential diagnosis of lung abnormalities (153).

Owing to its frequency and prognostic significance, the clinical, functional and radiological assessment of the respiratory system should be included in the work-up of all patients with SV, especially of those with AASV.

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