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The Respiratory System in Autoimmune Vascular Diseases

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Keywords

Granulomatosis with polyangiitis · Eosinophilic granulomatosis with polyangiitis · Microscopic polyangiitis · ANCA-associated vasculitis · Anti-glomerular basement membrane · Takayasu arteritis · Behçet disease · Respiratory system · Systemic vasculitis

Abstract

The respiratory system may be involved in all types of systemic vasculitis with varying significance and frequency. ANCA-associated vasculitis, including granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and microscopic polyangiitis, affects the respiratory tract more commonly than other vasculitis types. Granulomatosis with polyangiitis is always associated with upper or lower respiratory tract involvement. Pulmonary and ENT involvements are the hallmark feature of the disease and are present in 90 and 80% of cases, respectively, with frequent skin or gastrointestinal involvement. In about 10% of cases, the lung is the only organ affected. Eosinophilic granulomatosis with polyangiitis is always associated with hypereosinophilia and asthma which usually precedes the systemic manifestations by several years; however, onset of asthma and of the vasculitis may be concomitant. Parenchymal infiltrates may be migratory and rapidly resolve upon corticosteroid treatment. Diffuse alveolar hemorrhage and renal failure are typical features of microscopic polyangiitis. The former is the leading manifestation of anti-glomerular basement membrane disease and is usually part of a pulmonary-renal syndrome. Takayasu arteritis has a distinct clinical presentation due to pulmonary arteritis and may present with massive hemoptysis, chest pain, and rarely symptoms of pulmonary hypertension. Behçet disease is the most common cause of pulmonary artery aneurysm and can also cause in situ thrombosis of the pulmonary arteries. Corticosteroids and immunosuppressive agents are the mainstay of treatment. In conclusion, systemic vasculitis is a frequent cause of respiratory system involvement with diverse manifestations of distinct severity and outcome.

Previous articles in this series: 1. Lazor R, Nicod LP: The Lung in Rare Systemic Diseases. Respiration 2017;94:1. 2. Tran C, Barbey F, Lazor R, Bonafé L: Pulmonary Involvement in Adult Patients with Inborn Errors of Metabolism. Respiration 2017;94:2–13. 3. Borie R, Wislez M, Antoine M, Cadranel J: Lymphoproliferative Disorders of the Lung. Respiration 2017;94:157–175. 4. Dupuis-Girod S, Cottin V, Shovlin CL: The Lung in Hereditary Hemorrhagic Telangiectasia. Respiration 2017;94:315–330. 5. Uzunhan Y, Jeny F, Kambouchner M, Didier M, Bouvry D, Nunes H, Bernaudin J-F, Valeyre D: The Lung in Dysregulated States of Humoral Immunity. Respiration 2017;94:389–404. 6. Daccord C, Nicod LP, Lazor R: Cystic Lung Disease in Genetic Syndromes with Deficient Tumor Suppressor Gene Function. Respiration 2017;94:467–485.

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Introduction

The systemic vasculitides represent a heterogeneous group of systemic diseases that can affect vessels of all types. They have been recently reclassified and renamed during the international Chapel Hill consensus conference. Some eponyms were changed to more convenient, appropriate, and noneponymous names. Accordingly, Wegener granulomatosis and Churg-Strauss syndrome were renamed to granulomatosis with polyangiitis (GPA) and eosinophilic granulomatosis with polyangiitis (EGPA), respectively. However, the terminology of Behçet disease and Takayasu arteritis was maintained [1].

Vasculitides are divided into five main categories according to the size of the predominant vessels involved and the system affected (Table 1). This review will provide an update of the most recent publications regarding respiratory system manifestations in systemic vasculitides. It is not intended to comprehensively describe the general manifestations of systemic vasculitis but rather to present the diagnostic strategy of respiratory system involvement and to point out the main therapeutic challenges and options.

Table 1. Classification of systemic vasculitis according to International Chapel Hill Consensus Conference Nomenclature of Vasculitides

Vessel size	Vasculitis
Large-vessel vasculitis	Takayasu arteritis Giant-cell arteritis
Medium-vessel vasculitis	Polyarteritis nodosa Kawasaki disease
Small-vessel vasculitis	Granulomatosis with polyangiitis (GPA) Eosinophilic granulomatosis with polyangiitis (EGPA) Microscopic polyangiitis Anti-glomerular basement membrane (anti-GBM) Cryoglobulinemic vasculitis IgA vasculitis Hypocomplementemic urticarial vasculitis
Variable-vessel vasculitis	Behçet disease Cogan syndrome
Single-organ vasculitis	Cutaneous small-vessel vasculitis Testicular arteritis Central nervous system vasculitis

Granulomatosis with Polyangiitis

Presentation and Diagnosis

GPA is a multisystem vasculitis syndrome characterized by granulomatous lesions and necrotizing vasculitis [2]. All body organs may be affected. However, the upper and lower respiratory tract along with the kidneys are the most frequently involved organs (Tables 2–4) [3].

The annual incidence rate of GPA is variable across the world. About 8 cases/million are diagnosed yearly in the UK versus 15 cases/million in New Zealand [4, 5].

Pulmonary manifestations are present in 90% of cases with a broad clinical spectrum ranging from asymptomatic lung nodules or infiltrates to life-threatening alveolar hemorrhage [6]. Although manifestations can be variegated, distinguishing specific features is essential in treating GPA patients, as ultimately they have distinct prognostic and therapeutic implications. Lung manifestations may include, with decreasing frequency, lung nodules (89%), segmental bronchial wall thickening (56%), septal lines (38%), consolidations (30%), lobar bronchial wall thickening (28%), ground glass opacity (GGO) (26%), and bronchiectasis (19%) (Fig. 1–3). In addition, pleural effusion, pleural irregularities, hilar and mediastinal lymphadenopathy, and tracheal wall abnormalities are present equally in about 15% of cases [7]. Although uncommon, lymphadenopathy when present usually involves the right paratracheal and hilar nodes. Noncavitated nodules, consolidations, pulmonary infiltrates, and GGO are considered as mild parenchymal disease, whereas cavitated nodules and alveolar hemorrhage represent a more severe form requiring prompt clinical recognition with aggressive management [8, 9]. However, consolidation may progress to cavitated nodules or thick-walled masses. Bilateral variable-sized pulmonary nodules are frequently present, with typically fewer than 10 nodules and without regional predisposition. Cavitation is seen in almost half of patients. Upon treatment, nodules resolve, occasionally leaving a discoid scar as an end result. Around half of the patients have bilateral irregular high-density consolidations predominating in bronchovascular bundles and thus may mimicking organizing pneumonia. GGO are less commonly observed. A halo sign is present in 15% of cases [10–13].

Lung consolidation generally results from inflammatory pneumonia, alveolar hemorrhage, or lung infarction, while GGO represent alveolar hemorrhage or parenchymal infiltration with necrosis [14].

Diffuse alveolar hemorrhage (DAH) is rarely inaugural in GPA. In a series of 77 patients with GPA, alveolar

Table 2. Frequency of respiratory system involvement in systemic vasculitis

Vasculitis	Lung parenchymal	Laryngeal	Bronchial	Pleural	Nasal/ sinus	Pulmonary artery
Granulomatosis with polyangiitis	++++	++	+	+	+++	±
Eosinophilic granulomatosis with polyangiitis	++++	+	++++	++	+++	±
Microscopic polyangiitis	++	±	±	±	±	±
Anti-glomerular basement membrane	+++	±	±	±	±	±
Takayasu arteritis	±	+	±	++	+	+++
Behçet disease	+	+	±	+	++	+++

++++, very common; +++, common; ++, rare; +, reported; ±, extremely rare.

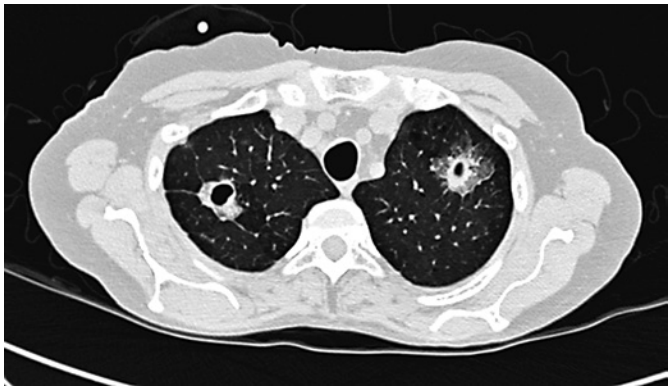

Fig. 1. Chest CT in a patient with granulomatosis with polyangiitis demonstrating thick-walled cavitated nodules in the upper zones of the lungs, with a halo of ground glass opacity surrounding the left-side nodule.

Table 3. Clinical symptoms of systemic vasculitis

Nasal	Crusting Congestion Epistaxis Rhinorrhea
Sinus	Headache Pain Discharge
Laryngeal	Dyspnea (initially inspiratory) Cough Stridor Voice change (if vocal cords are involved)
Bronchial	Dyspnea Cough Bronchorrhea Hemoptysis
Parenchymal	Chest pain Dyspnea Cough Hemoptysis
Pleural	Dyspnea Chest pain
Pulmonary artery	Chest pain Hemoptysis Dyspnea

hemorrhage was present in only 6 patients (7%) [10], and hemoptysis was present as the first presentation in 12% of 158 patients diagnosed with GPA. However, in this series, there were multiple causes for hemoptysis other than alveolar hemorrhage [2].

Panlobular or centrilobular emphysema may be occasionally seen in patients with GPA and may be associated with α-1-antitrypsin deficiency. Such an association has been described particularly in patients with anti-proteinase-3 (anti-PR3) anti-neutrophil cytoplasmic antibodies (ANCAs) [15–17]. In one study [16], the incidence and prevalence of GPA were increased by 10-fold in patients with severe α-1-antitrypsin deficiency when compared with the general population. Presumably, decreased α-1-antitrypsin level, endogenic proteins that neutralize proteinase activity, provoke autoimmunity in Pi ZZ and Pi SS phenotypes by producing anti-PR3 antibodies that have a crucial role in GPA pathogenesis that develops afterwards.

The pleura can also be involved. Pleural effusion is by far the most common pleural manifestation in GPA patients. Other pleural involvement may include pleuritis, pleural nodules, and pneumothorax [18].

Upper airway involvement was present in 95% of GPA patients during a 21-year follow-up study [19]. In anoth-

Table 4. Respiratory system manifestations according to vasculitis type

Vasculitis	Lung parenchymal	Laryngeal	Bronchial	Pleural	Nasal/sinus	Pulmonary artery
Granulomatosis with polyangiitis	Cavitated and noncavitated nodule/mass Consolidations Ground glass opacities Alveolar hemorrhage	Strictures and stenosis (usually subglottic) Ulcers Inflamed mucosa	Stenosis Bronchiectasis	Pleural effusion Pleural nodules Pneumothorax	Sinusitis Nasal mucosa ulcers Bone deformity Saddle nose Nasal mass	Inflamed vessel
Eosinophilic granulomatosis with polyangiitis	Consolidations Ground glass opacities Thickening of interlobular septa	Not reported	Asthma Stenosis Bronchiectasis	Pleural effusion	Nasal polyposis Eosinophilic rhinitis Chronic/recurrent rhinosinusitis	Not reported
Microscopic polyangiitis	Alveolar hemorrhage Subpleural reticulations Usual interstitial pneumonia pattern	Not reported	Not reported	Not reported	Sinusitis and nasal mucosa ulcers	Not reported
Anti-glomerular basement membrane	Alveolar hemorrhage	Not reported	Not reported	Not reported	Not reported	Not reported
Takayasu arteritis	Nodules Subpleural consolidations Infarction	Not reported	Endobronchial stenosis	Pleural effusion	Septal nasal perforation/saddle nose	Pulmonary artery stenosis and aneurysm Pulmonary hypertension
Behçet disease	Nodules Subpleural consolidations Infarction	Stenosis	Not reported	Pleural effusion	Not reported	Pulmonary artery aneurysm and in situ thrombosis Pulmonary hypertension

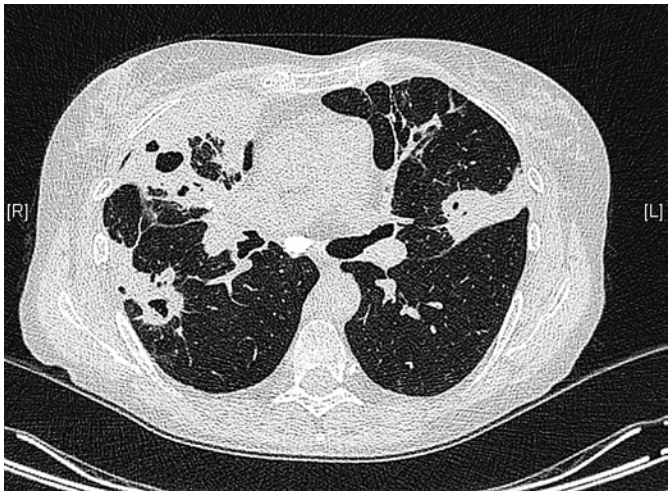

Fig. 2. Chest CT in a patient with granulomatosis with polyangiitis showing areas of consolidation, with cavitation within the consolidation and 1 thick-walled cavitated nodule.

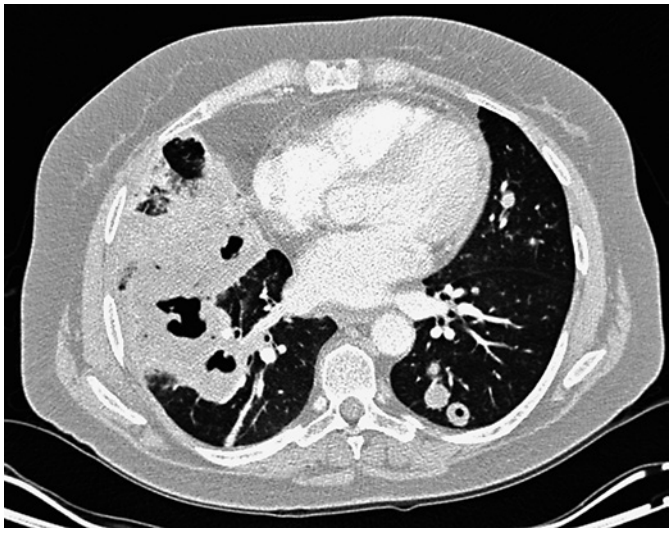

Fig. 3. Chest CT in another patient with granulomatosis with polyangiitis showing areas of consolidation, with cavitated nodules and cavitation within the consolidation.

er 20-year retrospective study, sinonasal manifestations were the most frequent upper airway involvement seen in 52% of GPA patients [20], consisting in rhinosinusitis, nasal mucosal ulceration, or saddle nose deformity.

Subglottic involvement is the most common site for large airway disease. Another etiology should be considered, as differentials include congenital, traumatic, infectious, and neoplastic causes; however, with no systemic manifestation. Symptoms develop gradually and include dry cough, hoarseness, and dyspnea. Tracheal stenosis is less frequent than endobronchial stenosis. Endobronchial involvement is more commonly bilateral than unilateral, and women are more commonly affected than men. Lesions of the main bronchi are almost multiple; lesions of secondary bronchi are bilateral in 39%, with left upper lobe involvement in two-thirds of cases [21]. Subglottic and tracheal involvement are primarily treated with local therapy (balloon dilatation, laser, cryotherapy, argon-plasma coagulation, diathermy, local injection of glucocorticoids, mitomycin C, and alemtuzumab have been used). Systemic therapy similar to that used for generalized or severe forms is reserved to those who do not respond to local interventions [21].

The American College of Rheumatology (ACR) criteria proposed in 1990 and intended for the classification of vasculitides are commonly used for the diagnosis of GPA since no diagnostic criteria have been validated despite major progress made in management since 1990 [22]. Although histology is fundamental to diagnose GPA and to rule out differentials, a biopsy is not always possible. The presence of at least 2 of 4 of the ACR criteria (i.e., nasal or oral inflammation, abnormal chest radiography, abnormal urinary sediment manifested as red blood cells/high power field or cell casts, and granulomatous inflammation on biopsy) yield a sensitivity of 88.2% and a specificity of 92% [22]. Till now, the diagnosis of GPA was based on clinical, radiological, and immunological findings. ANCAs have a crucial role to diagnose and differentiate GPA from other ANCA-associated vasculitides (AAVs). Anti-PR3 specificity is present in almost 90% of ANCA-associated GPA, while anti-myeloperoxidase specificity is present in less than 5% of cases [23]. Nevertheless, ANCA is not a substitute for the biopsy; it has an important role in suspected cases in particular when histological confirmation cannot be obtained. The role of ANCA positivity in predicting relapse is controversial [24–26]. ANCA positivity increases with disease damage and severity, ranging from about 5–10% of cases in localized forms to more than 90% of cases in cases with severe and systemic involvement.

Treatment

Treatment of GPA has dramatically evolved over the last two decades. It is divided into two phases: induction, when the disease is hit by high doses of corticosteroids combined with potent immunosuppressive drugs (cyclophosphamide or rituximab), followed by a maintenance phase when immunosuppressive treatment is prolonged to maintain remission. The maintenance phase has been the subject of multiple trials studying appropriate drugs and the ideal duration to prevent relapses. Nevertheless, a pretreatment assessment is mandatory in order to evaluate disease severity and not to overtreat clinical conditions that are not organ- or life-threatening. The Birmingham Vasculitis Activity Score/Wegener Granulomatosis Score is validated in GPA to categorize organ and system involvement into organ/life-threatening or not and to stratify treatment. Remission of disease is generally obtained using glucocorticoids associated with either cyclophosphamide (a pulsed intravenous regimen is preferred over the oral route due to the lower total cumulative dose of cyclophosphamide and reduced bladder-related complications) or rituximab, especially when the disease is organ- or life-threatening (e.g., sensorineural deafness, alveolar hemorrhage, or respiratory failure). In less severe cases with non-organ/life-threatening involvement, especially granulomatous disease involving the lung and the ENT sphere, remission may be induced using a combination of glucocorticoids with methotrexate (15–25 mg/week), or azathioprine (1–2 mg/kg/day), while mycophenolate mofetil (1.5–2 g/day) is less frequently used. Lower doses are used in elderly and less tolerant patients. When relapse occurs, reinduction usually follows the same principle as for the first induction but previous treatment, overall toxicity, organ damage, and infection risk should be taken into consideration.

Once remission is obtained, maintenance treatment aims at preventing relapses. Azathioprine and methotrexate are equally effective [27]. Rituximab has proved to be superior to azathioprine in decreasing relapse and sustaining remission with a similar frequency of severe adverse events at 28 months [28]. Mycophenolate mofetil is less effective than other maintenance treatments and therefore is only used when alternatives cannot be used or have been unsuccessful. Trimethoprim/sulfamethoxazole (800/160 mg twice daily) may reduce the risk of relapse especially in patients with sinonasal disease [29]. The remission maintenance therapy should be pursued for at least 2 years after the induction therapy for all AAVs [27].

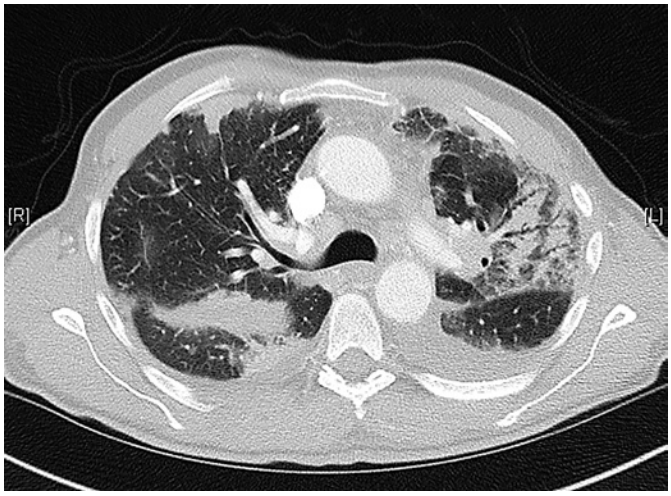

Fig. 4. Chest CT in a patient with eosinophilic granulomatosis with polyangiitis. Areas of consolidation, ground glass opacity, and air bronchogram correspond to eosinophilic pneumonia. Pleural effusion related to cardiac failure is also visible.

Eosinophilic Granulomatosis with Polyangiitis

Presentation and Diagnosis

EGPA is defined by an eosinophil-rich and necrotizing granulomatous inflammation involving the respiratory tract, with necrotizing vasculitis predominantly affecting small to medium-sized vessels, and associated with asthma and eosinophilia [1].

Historically, EGPA was considered as a disease evolving into three successive phases: a prodromal phase consisting of asthma commonly associated with allergic rhinitis, sinonasal polyposis, and recurrent rhinosinusitis; a second phase characterized by peripheral blood eosinophilia and/or eosinophilic organ infiltration; and a systemic vasculitis stage characterized by visceral organ involvement outside of the ear and respiratory system, especially polyneuropathy and skin involvement [30]. Nowadays, diagnosing EGPA does not mandate the presence of these consecutive stages as asthma may develop at the time or even years after the onset of the systemic vasculitis [31].

The annual incidence of EGPA is estimated to be 0.5–4.2/million persons with a prevalence of 11–14 cases/million inhabitants [32–34].

Recently, EGPA has been revisited as a disease with heterogeneous aspects of systemic involvement manifesting as granulomatous or vasculitis forms. ANCA, present in about 40% of cases, is seen as a dichotomous feature to separate these two forms. ANCA has anti-myeloperoxidase specificity in the majority of EGPA cases [35, 36]. Granulomatous forms usually lack ANCA positivity with more cardiac and pulmonary involvement; in contrast, vasculitic forms are characterized by ANCA positivity with renal involvement, mononeuritis complex, or vasculitic palpable purpura [35, 37]. Nevertheless, the ANCA identification is not sufficient for such categorization since it is present in only 40% of EGPA cases and one-third of ANCA-positive patients do not have genuine definitive or surrogate vasculitis features [36].

Asthma is considered a sine qua none as almost all patients with EGPA have had or develop asthma during the disease course. Typically, asthma is severe, corticosteroid dependent, and precedes the systemic manifestations of EGPA by several years. Women have a longer duration of asthma before EGPA diagnosis than men [35, 36]. The severity of asthma typically increases 3–6 months before the beginning of systemic manifestations [38]. Data regarding asthma outcome are controversial. Szczeklik et al. [39] reported that asthma severity decreased in the 2 years after achieving vasculitis remission. Yet, we have recently demonstrated unchanged asthma severity in 80% of patients following disease remission after several years of follow-up [38]. In this study, a significant number of patients had criteria for EGPA with hypereosinophilic asthma and systemic manifestations but not corresponding to overt polyangiitis. Therefore, a new nomenclature of hypereosinophilic asthma with systemic manifestations (HASM) was proposed to identify patients without proven vasculitis (*polyangiitis*) [36].

Typically, patients with EGPA present with eosinophilic pneumonia (Fig. 4), which may resolve very rapidly upon corticosteroid treatment; pleural effusion due to eosinophilic pleural involvement or transudates related to cardiac failure may be associated. Studies describing pulmonary manifestations in EGPA demonstrate a variety of imaging features. In one short series of patients with lung involvement, GGO were seen in all patients, centrilobular nodules with GGO in 89%, peribronchovascular consolidations with lower lung zone predominance in 56%, small and moderate-size nodules in 44%, and interlobular septal thickening in 22% of patients [40]. In a study of 157 patients with EGPA, we found parenchymal manifestations in decreasing order of frequency: GGO (39%), bronchial wall thickening (32%), consolidations (28%), micronodules less than 3 mm (24%), bronchial dilatation (15%), centrilobular nodules less than 10 mm (14%), and nodules up to 30 mm (11%). Other manifestations such as air trapping, mosaic attenuation, halo sign, and masses were seen in less than 10% of cases [38].

Table 5. Current nomenclature of eosinophilic granulomatosis with polyangiitis and proposed nomenclature of hypereosinophilic asthma with (any) systemic manifestations

Proposed nomenclature: eosinophilic granulomatosis with polyangiitis	Proposed nomenclature: hypereosinophilic asthma with systemic manifestations
Definite vasculitic features – Biopsy-proven necrotizing vasculitis of any organ – Biopsy-proven necrotizing glomerulonephritis or crescentic glomerulonephritis – Alveolar hemorrhage – Palpable purpura – Myocardial infarction due to proven vasculitis	– Any systemic manifestations other than definite polyangiitis or mononeuritis *and* – Absence of ANCA
Definite surrogates of vasculitis – Hematuria associated with red casts or >10% dysmorphic erythrocytes *or* hematuria and 2+ proteinuria on urinalysis – Leukocystoclasic capillaritis and/or eosinophilic infiltration of the arterial wall at biopsy	
Mononeuritis or mononeuritis multiplex	
ANCA and any systemic manifestations	

Interestingly, migratory infiltrates, a characteristic sign, were seen in less than 10% of cases compared to 40% of cases in Lanham's series [41]. In contrast to GPA patients, cavitation has not been reported in EGPA. Pleural effusion, secondary to heart failure or to direct eosinophilic involvement, is observed in 12% of cases [38]. Although extremely rare, alveolar hemorrhage has been reported in EGPA [42–47].

Sinonasal disease is very common. In a study of 28 patients, Bacciu et al. [48] observed nasal polyposis and allergic rhinitis in 76.1 and 42.8%, respectively. A history of chronic rhinosinusitis was found in 14.2% of patients. In another series of 29 patients, Bacciu et al. [49] reported nasal polyposis in 17 patients (58.6%). Lund and Mackay have reported on endoscopic scoring system and observed grade III nasal polyposis in 9 cases (52.9%), grade II in 6 cases (35.2%), and grade I in the remaining 2 cases (5.8%) [142]. We found a history of chronic rhinosinusitis in 114 patients (73%) divided into allergic (21%) and nonallergic (52%), while nasal polyposis was present in 83 patients (53%), with half of them requiring surgery [38]. Laryngeal or airway involvement has not been reported in EGPA patients.

Although based on a series of 16 patients, Lanham's criteria remain the only established diagnostic criteria for EGPA, consisting of a history of asthma, peripheral hypereosinophilia, and ≥2 nonpulmonary eosinophilic tissue infiltrations [41]. Noteworthy, perinuclear ANCAs (p-ANCAs) with myeloperoxidase specificity, which were not available at the time of the study by Lanham et al. [41], are not part of these criteria; however, when present, they contribute to confirm the diagnosis, and have been considered as an additional surrogate marker for EGPA. We have proposed working criteria for EGPA, which need external validation, and proposed a new nomenclature of EGPA with systemic vasculitic manifestations (Table 5). As a result, we suggested that hypereosinophilic (eosinophils >1.5 g/L) asthma patients with systemic nonvasculitic manifestations to be called Hypereosinophilic Asthma with (any) Systemic (nonvasculitic) Manifestations (HASM) instead of EGPA. In contrast, the former terminology of EGPA would be better reserved for those who present genuine *vasculitic* manifestations [36].

Treatment

Treatment of EGPA was addressed in recent recommendations by the European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA) recommendations and by a dedicated taskforce [27, 50]. Treatment follows the same principle as for all AAVs; however, the level of evidence and the grade of recommendation are lower for EGPA than for other AAVs. Patients without severity criteria do not require intravenous cyclophosphamide. In addition, azathioprine is the only im-

munosuppressive drug recommended for remission maintenance [27]. Rituximab has not yet been evaluated in patients with EGPA.

Microscopic Polyangiitis

Presentation and Diagnosis

Microscopic polyangiitis (MPA), with few or no immune deposits, predominantly affects small-size vessels. Necrotizing arteritis involving small and medium arteries may also be present. Pulmonary capillaritis often occurs. Inflammation that is not centered on vessels, including granulomatous inflammation, is absent [1]. Although in 1990 MPA was not addressed in the ACR classification, it is now well individualized and an entity distinct from periarteritis nodosa. While still not final, new classification criteria for AAVs are currently under revision by ACR/EULAR.

The prevalence of MPA, as that of GPA, varies between countries. The annual incidence has been estimated to be 18.2 cases/million in Japan and 6.5 cases/million in the UK. There is no gender predominance. The mean age at diagnosis is 69 years in Japan and 60 years in the UK [51].

Pulmonary manifestations in MPA are unique among other AAVs and are dominated by DAH. It ranges from asymptomatic GGO found incidentally on computed tomography (CT) of the chest to a full-blown acute DAH with respiratory failure. In most patients with MPA, pulmonary manifestations are solely represented by DAH of varying severity, with acute or subacute onset; occasionally patients may present with chronic occult DAH at imaging, with hemosiderophages found at bronchoalveolar lavage.

In a large study of 167 patients with MPA in Japan using chest CT, 97% of them had at least one CT abnormality. Interstitial lung abnormalities were found in 66%: GGO in 41%, a reticular pattern in 41%, interlobular septal thickening in 41%, consolidation in 23%, and honeycombing in 23% of patients. In addition, some airway abnormalities were seen in 66% of patients, described as bronchiolitis (55%), bronchial wall thickening (44%), and bronchiectasis (32%). Pleural lesions were also reported in 53% of cases and described as pleural thickening in 34% and effusion in 26% of cases [52]. Another series of 40 patients reported that pulmonary complaints and infiltrates were present in 80 and 92% of patients, respectively [53]. In contrast, Hassan et al. [54] demonstrated that pulmonary involvement was present in only 15% of cases, which seems to be more representative of patients as seen in the clinic (in pulmonary, nephrology, neurology, and dermatology departments), whereas studies were based on the International Classification of Diseases, ninth revision (ICD-9) code of vasculitis.

DAH is the most frequent and symptomatic presentation in MPA. Its prevalence varies between 10 and 30% depending on the methods used to diagnose DAH and the referral pattern (pulmonology, nephrology, or internal medicine departments) [55, 56]. In most cases, DAH develops acutely manifesting as dyspnea with or without hemoptysis; it may also follow an indolent course with occasional hemoptysis and fleeting GGO on chest imaging [57]. DAH is frequently the first manifestation of the disease; in one study, DAH occurred at first presentation in 86.8% of cases and assisted ventilation was required in 36 patients (67.9%) [58].

In a series of 29 patients with MPA and DAH, mostly from respiratory departments, glomerulonephritis was present in 28 patients (97%), while fever was present in 62%, and myalgia and arthralgia in 50% of cases [57]. Yet, isolated alveolar hemorrhage has been reported [59]. In a large study of 824 patients with AAVs, DAH was present in 53 patients; all but one had renal involvement.

The clinical manifestations of DAH are mainly dyspnea and cough; hemoptysis is not always present, and therefore absence of hemoptysis does not rule out the diagnosis of DAH. Multiple diagnostic modalities for DAH have been used according to the test availability, patient clinical severity, and the level of suspicion. Although being considered as a gold standard for DAH, surgical lung biopsy is no longer used due to the invasive nature of the biopsy, the risk inherent to the test, and the frequent lack of histological features associated with etiology [60]. Nevertheless, when other less invasive modalities (clinical and paraclinical studies) fail to recognize DAH etiology, video-assisted lung biopsy may exceptionally be discussed. Fiberoptic bronchoscopy and bronchoalveolar lavage are crucial for DAH diagnosis (Fig. 5). The presence of increased bloody appearance on subsequent aliquots is specific for DAH and is the best diagnostic test; when DAH has started ≥2 days earlier, the presence of hemosiderin-laden alveolar macrophages (siderophages) ≥20% can confirm the diagnosis of DAH; siderophages can be quantified using the Golde score, where a score >100 is confirmative and obviates the need for other diagnostic interventions [61, 62].

When typical, high-resolution CT (HRCT) of the chest shows bilateral alveolar opacities, with central predominance and peripheral spearing near the pleura, that may

be associated with GGO; alveolar opacities progress to GGO within days. Other CT findings that mimic decompensated left heart failure may be seen as well [63, 64]. A dropped hemoglobin level may serve as surrogate for recent alveolar hemorrhage. Increased carbon monoxide diffusion observed in recent DAH however lacks specificity and sensitivity.

Whether MPA can directly cause pulmonary fibrosis is still controversial; however, subtle interstitial lung abnormalities may frequently be found on chest CT. Recently, attention has also been given to a particular presentation of MPA consisting of pulmonary fibrosis associated with ANCA, especially with myeloperoxidase specificity, with occasional progression to systemic vasculitis especially with renal involvement. In a long-term retrospective study over a 15-year period in 28 patients with MPA, pulmonary fibrosis was identified in 9 patients (32%) and DAH was present in 11 cases (39%). A definite or possible usual interstitial pneumonia pattern was present in 8 cases (88%) and was associated with poor prognosis [65]. In another study of interstitial pneumonia with anti-myeloperoxidase-ANCA, 8 patients had a usual interstitial pneumonia pattern accompanied by areas of nonspecific interstitial pneumonia pattern and 1 patient had diffuse alveolar damage [66]. Pulmonary fibrosis may precede other disease manifestations by a range of 5–108 months, but would not occur after the diagnosis of MPA [65, 67]. The prognosis of MPA with pulmonary fibrosis is worse than that of MPA without pulmonary fibrosis and seems to be better than that of patients with idiopathic pulmonary fibrosis [65, 67, 68].

Sinonasal manifestations are less common in patients with MPA than in those with GPA or EGPA. Moreover, sinus bone destruction has not been observed in MPA patients [69].

ANCA is positive in 95% of cases. Anti-myeloperoxidase specificity is present in 70%, while the remaining cases have anti-PR3. In MPA, reappearance of anti-myeloperoxidase in previously treated patients after being negative is strongly associated with a relapse, with a positive predictive value of 90% and a negative predictive value of 94% [70]. ANCA titer may therefore be monitored once the remission has been obtained.

Treatment

The treatment of MPA mirrors that of GPA. To induce remission, patients are treated with pulsed glucocorticoids (1 g/day for 3 days) followed by oral corticosteroids and pulsed intravenous cyclophosphamide. Plasma exchanges are used in severe forms of DAH or acute renal failure. Daily full plasma volume apheresis has been used in severe cases with successful results along with adjunctive mechanical ventilation [71].

Fig. 5. Aspect of the bronchoalveolar lavage fluid in a patient with microscopic polyangiitis and diffuse alveolar hemorrhage.

Anti-Glomerular Basement Membrane Disease

Presentation and Diagnosis

According to the international Chapel Hill consensus conference definition, anti-glomerular basement membrane (GBM) disease is a systemic vasculitis affecting glomerular capillaries, pulmonary capillaries, or both, associated with basement membrane deposition of anti-basement membrane autoantibodies. Lung involvement causes pulmonary hemorrhage, and renal involvement causes glomerulonephritis with necrosis and crescents [1]. The term anti-GBM disease had replaced that of Goodpasture disease or syndrome after it had been used for a long time to describe DAH and glomerulonephritis associated with anti-GBM antibodies. However, the term anti-GBM disease is also a misnomer since the anti-GBM antibodies are reactive against alveolar capillary basement membrane causing alveolar hemorrhage as well as GBM causing glomerulonephritis or hematuria. As demonstrated by the landmark study of Lerner et al. [72], these antibodies had nephritogenic properties in developing immediate glomerulonephritis and pulmonary hemorrhage in recipient monkeys once infused by circulating or kidney-bound GBM antibodies. The anti-GBM antibodies, primarily IgG of IgG1 and IgG4 isotypes, target the collagen type IV molecule, which is the major constituent of all basement membranes. Type IV collagen (family of 6 alpha chains) is formed of a short N-

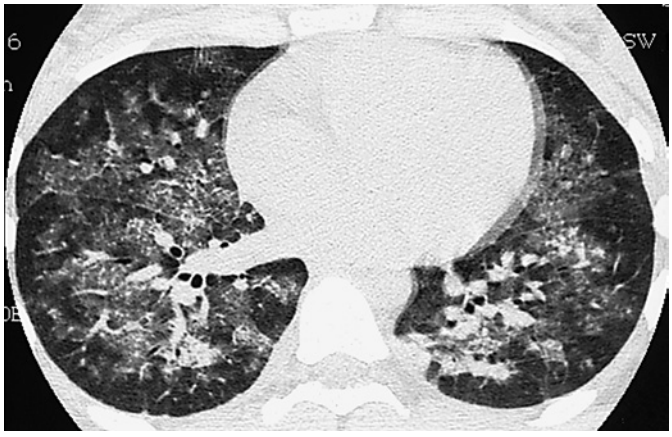

Fig. 6. Chest CT demonstrating diffuse ground glass attenuation due to diffuse alveolar hemorrhage in a patient with anti-glomerular membrane disease.

terminal noncollagenous region, a long collagenous region, and a globular C-terminal noncollagenous (NCI) domain. The NCI domain of the α3 chain is the main antigen recognized by the autoantibody; however, some antibody-binding to other α chains (α1, α2, α4, and α5) has been observed due to cross-reactivity. Although the α3 (NCI) chain is expressed in the basement membrane of the glomeruli and the alveoli as well as in the basement membranes of other systems (i.e., seminiferous tubules, choroid plexus, cochlea, and lens capsule), the clinical manifestations are limited to the kidney and lung. This preferential binding is believed to be related to the presence of fenestration (within alveoli and glomeruli) that allows a higher number of antibodies to be infiltrated [73, 74].

Anti-GBM disease is a rare autoimmune vasculitis with an incidence of 0.5–1 million persons/year [75, 76]. It follows a bimodal peak-age pattern. The first peak occurs predominantly in men during the second and third decades and manifests mainly as DAH. The second peak predominates in women in the sixth and seventh decades and more often involves renal-limited disease [77]. Pulmonary-renal syndrome is the typical manifestation of anti-GBM disease; however, isolated alveolar hemorrhage or glomerulonephritis has been reported [78, 79].

DAH is by far the most predominant respiratory manifestation in anti-GBM disease (Fig. 6). In a study of 28 anti-GBM patients with DAH diagnosed using bronchoalveolar lavage, chest radiography showed abnormalities in 86% of patients [80]. Lower lung fields were more frequently involved than upper lung fields, 68 versus 46%, respectively. HRCT was performed in only 20 patients, showing abnormalities in 80% of them. GGO and consolidations were observed in 55 and 40% of cases, respectively, whereas nodules were seen in only 20% of cases. In this study, circulating anti-GBM antibodies were present in two-thirds of cases and linear IgG deposits along GBM as well as linear IgG deposits along alveolar basement membrane were detected in all patients tested (23 and 5 cases, respectively). p-ANCAs were positive in 2 patients without signs of systemic vasculitis other than the pneumo-renal syndrome [80]. A case series of 10 patients with anti-GBM disease revealed pulmonary-renal manifestations in 6 patients, and the disease was limited to renal involvement in the remaining 4 patients. Anti-GBM antibodies were present in all cases.

Although this condition is associated with anti-GBM antibodies that play a crucial role in pathophysiology, ANCAs may occasionally be found. In one series of 10 patients, anti-PR-3 and anti-myeloperoxidase ANCAs were present in 2 and 1 cases, respectively [81]. Data regarding renal outcome in patients with double positivity (anti-GBM antibodies and proteinase 3/myeloperoxidase ANCA) are controversial [82–84]. Whether double positivity affects the pulmonary outcome is unknown.

The diagnosis of anti-GBM disease is based on the detection of circulating or tissue-bound (kidney or lung-bound) anti-GBM antibodies. Enzyme-linked immunosorbent assay (ELISA), western blotting, or indirect immunofluorescence are used to detect circulating antibodies. Importantly, low levels of circulating anti-GBM antibodies cannot be detected by indirect immunofluorescence. Kidney biopsy is the usual site to demonstrate tissue-bound antibodies that characteristically shows linear fluorescence on kidney tissue. Lung biopsy is invasive, less sensitive, and therefore seldom performed when a diagnosis of anti-GBM antibody syndrome is considered. Whenever present together with typical clinical manifestations, circulating or kidney-bound anti-GBM antibodies are confirmatory of the diagnosis. On the other hand, not all patients with anti-GBM disease have circulating anti-GBM antibodies; false positive kidney-bound anti-GBM may be found especially in patients with diabetes. In some cases, tissue-bound antibodies may be lacking despite the presence of circulating antibodies. Such a situation is present when the typical linear fluorescence seen in anti-GBM disease is not seen due to severe glomerular destruction or in the presence of immunoglobulin or complement deposits carried by another autoimmune process.

Treatment

Anti-GBM disease is a severe autoimmune disease that should be treated promptly and aggressively to decrease production, enhance clearance, or remove circulating autoantibodies, with the goal of preventing definitive renal failure and to reduce the risk of relapsing severe DAH.

Corticosteroids (250 mg/day for 3 consecutive days followed by prednisone 1 mg/kg) and intravenous cyclophosphamide pulses (750 mg/m^2 every 3–4 weeks) represent the mainstay of the treatment strategy to halt neutrophil-driven inflammation and to cease antibody production, respectively. If initially positive, circulating anti-GBM antibodies should be checked every 1–2 weeks until a negative result is obtained on two occasions. If antibodies remain positive, an immunosuppressive regimen should be pursued for 6–9 months.

Plasma exchange is rapidly effective to wash out serum from circulating autoantibodies. It is generally recommended as an adjunctive treatment modality for patients with anti-GBM disease. Both daily and alternate-day regimens are accepted. The duration is usually for 2 weeks at least and is modulated according to the clinical status and the level of circulating autoantibodies [85, 86]. Rituximab has been used successfully in severe acute as well as in refractory or relapsing disease [87, 88].

Takayasu Arteritis

Presentation and Diagnosis

Takayasu arteritis and giant cell arteritis are the two systemic vasculitides that target the large vessels. They share the same histological features and therefore differentiation using biopsy is impossible; nevertheless, they are considered distinct vasculitis diseases based on distinct clinical features.

Takayasu arteritis is a systemic arteritis, often granulomatous predominantly affecting the aorta and/or its major branches [1]. Takayasu arteritis was first described by Mikito Takayasu, a Japanese ophthalmologist in 1908, in a patient with retinal vasculitis manifested as coronary anastomosis of the retinal vasculature [89].

Takayasu arteritis usually affects patients younger than 50 years, with female predominance and some ethnic predisposition. The prevalence is highly variable among regions and was estimated at 40/million in Japan, 4.7/million in the UK, 9/million in the USA, 6.4/million in Sweden, and 12.8/million in Turkey [90–94].

Clinical manifestations are variable according to the involved vessel/organ and time of presentation. The early phase ("pre-pulseless" phase) is characterized by systemic, nonspecific symptoms such as fatigue, fever, arthralgia, headache, anorexia, weight loss, and rash. The later "pulseless" phase of the disease is characterized by vascular bruits, diminished or absent pulses, hypertension, mesenteric ischemia, neurological manifestations, and limb claudication [95].

The pulmonary artery is the second large artery involved in Takayasu arteritis following the aorta. The incidence of pulmonary artery involvement varies between 41 and 100% [96, 97]. Sharma et al. [98] studied 44 asymptomatic Indian patients with Takayasu arteritis for pulmonary artery involvement using intravenous digital subtraction angiography; only 6 patients (14.3%) had evidence of pulmonary artery involvement. Such a finding might be due to the low sensitivity of this method to detect nonocclusive pulmonary artery/branches stenosis or to a variable incidence of pulmonary artery involvement in Indian populations [98].

CT imaging of pulmonary arteries in Takayasu arteritis patients may reveal pulmonary artery aneurysm, diffuse or segmental parietal thickening, pulmonary artery thrombosis, or perfusion mosaic aspect [99]. Other pulmonary manifestations include nodular infiltrates, massive pulmonary hemorrhage, and pleural effusion [100–103].

Clinical manifestations related to pulmonary artery involvement are nonspecific. Chest pain, shortness of breath, hemoptysis, and cough are most commonly reported [104]. Interestingly, recurrent pulmonary infarction/embolism and pulmonary hypertension (PH) are characteristic complications of Takayasu arteritis [105–107].

PH is present in 12% percent of Takayasu arteritis patients [108]. A prospective study comparing patients with Takayasu arteritis and PH, Takayasu arteritis with pulmonary artery involvement but no PH, and patients with idiopathic pulmonary arterial hypertension found that those with Takayasu arteritis and PH had lower mean cardiac indexes than their counterparts without PH. All patients with Takayasu arteritis and precapillary PH had a positive acute vasoreactivity response versus 33% of patients with idiopathic pulmonary arterial hypertension. Among patients with Takayasu arteritis and PH, 25% had PH due to left heart disease rather than pulmonary artery involvement [107].

In addition to pulmonary artery involvement and PH, Takayasu arteritis may cause septal nasal perforation, saddle nose deformity, and endobronchial involvement [109–111].

In 1988, Ishikawa [112] proposed a set of classification criteria for patients with Takayasu arteritis, based on 2

major and 9 minor criteria as well as an obligatory criterion. In addition to the obligatory criterion (i.e., age ≤40 years), the diagnosis of Takayasu arteritis mandates the presence of 2 major, or 1 major and ≥2 minor, or ≥4 minor criteria [112]. In 1990, the ACR developed a set of classification criteria to better characterize Takayasu arteritis and to differentiate it from other systemic vasculitides [113]. Interestingly, when the Ishikawa and ACR sets of criteria were tested in Indian patients with documented Takayasu arteritis, they yielded a sensitivity of 60.4 and 77.4%, respectively, and the specificity was >95% for both [114]. The main criticism for both criteria was the age limitation. The modified Ishikawa criteria removing the age criterion have a higher sensitivity (92.5%) and specificity (95%) [114, 115], and therefore represent the currently used diagnostic criteria for adults suspected to have Takayasu arteritis.

Treatment

Due to the rarity of Takayasu arteritis and the lack of international collaborative studies on this condition as compared to other systemic vasculitides, treatment modalities are proposed based on clinical observations and experts' opinions. Corticosteroids are the mainstay and immunosuppressors (methotrexate, azathioprine, leflunomide, cyclophosphamide, and mycophenolate mofetil) are usually added. TNFα antagonists and tocilizumab (a monoclonal antibody targeting IL-6) have been used as well [116].

Catheter-based interventional therapy such as percutaneous transluminal pulmonary angioplasty and balloon pulmonary angioplasty have been used successfully in patients with Takayasu arteritis and PH due to pulmonary artery stenosis [117]. Stent implementation has also been used with no restenosis during a 3-year follow-up period [118].

Behçet Disease

Presentation and Diagnosis

Behçet disease is a multisystem disease in which most body organs can be involved. Its name dates back to Hulusi Behçet, a Turkish dermatologist who described it as a triad of uveitis, oral, and genital ulcers [119]. The epidemiology of Behçet disease is quite variable. Although it has been reported in most areas of the world, it is by far more common in Japan, Iran, and most of the Mediterranean countries. Men are more commonly affected than women, with greater severity in men and individuals between 20 and 40 years of age. Clinical manifestations are characterized by and not limited to oral aphthosis (95%), genital aphthosis (60–90%), pseudofolliculitis (called also Behçet pustulosis), erythema nodosum (40–90%), and uveitis (45–90%). Gastrointestinal, neurological, vascular, and articular manifestations are less commonly seen. In addition, manifestations are somehow different among age groups affected and among countries [120–122].

Diagnostic criteria were initially set by the international study group including physicians of 7 countries [123]. A recurrent oral aphthous lesion at least 3 times during the last 12-month period was a prerequisite criterion to establish the diagnosis, although the study group believed that this may be absent in 2–3% of patients [123]. In 2013, international experts revised the diagnostic criteria for Behçet disease and proposed a score to diagnose Behçet disease, with a score of ≥6 points invariably required for Behçet disease, among ocular lesions, oral aphthosis, genital aphthosis (2 points each), other skin lesions, neurological manifestations, vascular manifestations, and positive pathergy test (1 point each) [124].

The respiratory system is frequently involved. Besides oral lesions, the lungs represent the most frequently affected organ in term of frequency and morbidity. The underlying mechanism is related to its vasculitic pathology.

Behçet disease is a variable-vessel vasculitis that can affect vessels of any size (small, medium, and large) and type (arteries, veins, and capillaries) [1]. Hence, Behçet disease shares manifestations of all types of vasculitis in addition to the predominant involvement of pulmonary arteries. Although much rarer than then involvement of pulmonary arteries, nose and throat involvement has been also reported.

Whilst rare, involvement of pulmonary arteries is responsible for the main morbidity and mortality associated with Behçet disease. Pulmonary artery aneurysms and in situ pulmonary artery thrombosis are present in two-thirds and one-third of cases with involvement of the pulmonary arteries, respectively, affecting less than 5% in the general Behçet cohort [125–127]. However, involvement of pulmonary arteries is two times more frequent in patients with Behçet disease who have other vascular involvement, especially deep venous thrombosis, an association which may be due to the histological properties of pulmonary arteries and their resemblance to the venous system and especially the vena cava. Therefore, pulmonary arteries are considered as a continuum of the vena cava [128]. On the other hand, lower extremity deep vein thrombosis and right-sided intracardiac thrombosis are present in 80 and 30% of patients with involvement of pulmonary arteries, respectively [129].

Clinically pulmonary artery aneurysm and in situ thrombosis are indistinguishable. Yet, hemoptysis is less frequent and less abundant in in situ pulmonary artery thrombosis. In a series of 47 patients with Behçet disease and pulmonary artery involvement, hemoptysis was the most common presenting symptom (79%). Other pulmonary symptoms such as cough, dyspnea, and chest pain were less frequent. In this study, the descending branches of the pulmonary arteries were the most commonly involved [129].

In addition, chest CT in patients with Behçet disease may reveal peripheral and subpleural nodules/consolidations and cavities representing pulmonary infarction or hemorrhage. Nodules dominate in the acute phase of the disease, whereas cavities are more commonly found in the chronic phase [130, 131]. Additional features include mild bronchiectasis, atelectasis, fibrosis, and emphysema. The last two findings result from regeneration and loss of damaged lung tissue. Focal or diffuse air trapping may also be seen [132, 133].

Laryngeal and hypopharyngeal involvement are the most common features of ENT involvement. Pharyngeal stenosis and ulceration have been reported. Patients present with dysphagia due to edema of the laryngopharyngeal wall, whereas those with laryngeal involvement present with dyspnea, dysphagia, and pain during speech that may radiate to the ear [134–137].

Treatment

Survival of Behçet disease patients is related to pulmonary artery involvement and Budd-Chiari syndrome. Immunosuppressors are the mainstay of treatment for both pulmonary artery aneurysm and in situ thrombosis and may result in the resolution of arterial lesions in up to 70% of cases. An accepted regimen for pulmonary artery involvement is pulse corticosteroid therapy (1 g every day for 3–5 consecutive days) followed by prednisolone of 1 mg/kg tapered and stopped over 6 months. Cyclophosphamide is usually added to corticosteroids and continued as a monthly intravenous 1-g infusion for 6–12 months. If remission is obtained, azathioprine or mycophenolate mofetil may be used as maintenance therapy. In refractory cases, anti-TNF agents might be used [138–140]. Anticoagulation is still a matter of debate in this regard, especially in the presence of pulmonary artery aneurysm, which eventually may lead to life-threatening complications such as pulmonary artery rupture. However, anticoagulation has been proven effective in preventing recurrence [141].

Conclusion

Respiratory system involvement is relatively frequent in anti-GBM disease, Takayasu arteritis, and Behçet disease, while in GPA and EGPA it is the most common system involved. In AAVs as well in Behçet disease, survival is related to pulmonary involvement. Therefore, recognition of respiratory manifestations may help to establish an early diagnosis, especially when characteristic features are found (e.g., pulmonary artery involvement, subpleural nodules with localized subpleural emphysema and fibrosis, cavitated nodules, laryngopharyngeal stenosis/ulceration) and hence to avoid disease progression and eventually increased morbidity and mortality. Pulmonary vasculitides often present with life-threatening complications rendering usual diagnostic procedures extremely difficult. In AAVs, ENT involvement is often associated with a better prognosis but a relapsing disease. In GPA, nodules, consolidations, and excavated masses are the predominant pulmonary features. In addition, asthma is a sine qua none for diagnosis of EGPA, while in MPA alveolar hemorrhage predominates. In anti-GBM disease and MPA, alveolar hemorrhage is the prototype of respiratory system involvement and can occur in all the vasculitides. Takayasu arteritis and Behçet disease are characterized by pulmonary artery involvement leading to aneurysms, PH, and in situ thrombosis. Corticosteroids are the cornerstone of therapy for these vasculitides. Immunosuppressors are usually used to induce remission and as a maintenance therapy to prevent relapse. Recently, some new drugs have demonstrated to be efficacious and safe, including rituximab in GPA and anti-GBM disease or anti-TNF agents in Takayasu arteritis and Behçet disease. Plasmapheresis remains an adjunctive and very effective tool for severe alveolar hemorrhage, especially in anti-GBM disease. Vascular interventions are effective in Takayasu arteritis for pulmonary artery thrombosis and PH.

Recent progress in the assessment and management of systemic vasculitides has improved survival, although morbidity and mortality remain significant and predominantly related to pulmonary involvement, and immunosuppression. Further studies are needed to develop treatment approaches associated with both better efficacy on refractory cases and long-term tolerability.

Disclosure Statement

The authors declare no conflict of interest for this paper.

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