

Review

Pulmonary pathology in vasculitis

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Summary

Pulmonary involvement is frequent in vasculitis, particularly in ANCA-associated small vessel vasculitis. Laboratory and radiological data alone are often sufficient to confirm the clinical hypothesis, but sometimes the pathologist plays a crucial role in the differential diagnosis and the patient's management. In this review, the pathologic features of pulmonary vasculitis and the pathologist's role in this field are illustrated.

Key words: vasculitis, granulomatosis with polyangiitis, pathology, lung

Introduction

Pathologic diagnosis of pulmonary vasculitis is a complex and challenging issue due to the following reasons:

- Vasculitides are rare, and very few pathologists deal with a sufficient number of cases to develop an adequate experience.
- The classification of vasculitis is based on the recognition of well-defined clinical-pathological entities ¹. The diagnosis is rarely reached by the pathologist alone, and the importance of the pathologist's contribution varies depending on the case.
- When the term vasculitis is used, it should be clarified whether in a *histological* or in a *clinical* sense because the meanings do not always overlap.
- Histologically, vasculitis is defined as a transmural inflammation of the vessel, with some damage to the vascular wall. This histology may be seen in vasculitic syndromes but is also encountered in non-vasculitic diseases, including infection, when vessels are involved by a surrounding inflammatory process. Moreover, the pathologist can support a diagnosis of vasculitis even in the absence of *histologic* vasculitis. This is encountered in granulomatosis with polyangiitis when the biopsy shows the characteristic necrotizing parenchymal lesions, and in vasculitic acute and organizing alveolar hemorrhage syndromes with histologic alveolar hemorrhage.
- The clinical manifestations and the histologic spectrum of vasculitis are broad, sometimes overlapping with different diseases, rendering the differential diagnosis challenging.
- Perivascular inflammation, not extending into the vascular wall, is a common non-specific finding and should not be interpreted as indicative of vasculitis. The distinction between a non-specific perivascular inflammation and a genuine vasculitis is generally straightforward but occasionally is quite subjective.

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- Sampling is an important issue: the characteristic histologic lesions of vasculitis are often focal, and biopsies should be sufficiently large and deep to increase the probability of diagnosis. Moreover, vasculitis is a dynamic process and its histologic appearance changes over time: biopsies are generally more informative when they are performed in the active phase of the disease.

Vasculitis is classified based on size of the vessel involved ¹. Pulmonary involvement is frequent in ANCA-associated small-vessel vasculitis (granulomatosis with polyangiitis, eosinophilic granulomatosis with polyangiitis, and microscopic polyangiitis), but may occur with a lower frequency in other vasculitides.

This review illustrates the pathologic features of pulmonary vasculitides and the pathologist's role in this field.

Granulomatosis with polyangiitis

CLINICAL AND LABORATORY FEATURES

Granulomatosis with polyangiitis (GPA), formerly known as Wegener's granulomatosis, is a systemic disease that can affect individuals of both sexes and any age, including pediatric patients, with an average age at diagnosis of about 50 years. The disease is rare, with a prevalence of 3 per 100,000 ².

The clinical manifestations are protean ³⁻⁵. At the onset, the upper respiratory tract is usually involved. Sinusitis, nasal ulcerations, septal perforation, cartilage destruction, nasal obstruction and epistaxis are frequent presenting symptoms. The combination of septal perforation and cartilage destruction may lead to the characteristic "saddle nose" deformity with collapse of the bridge of the nose at the junction between the nasal bone and the cartilage. Ear involvement is not rare and may lead to otitis media followed by hearing loss. Pulmonary localization is common, affecting 45% of patients at the disease onset and over 85% during the clinical course. It generally manifests with chronic cough, dyspnea, and chest pain, but some patients present acutely with the clinical features of diffuse alveolar hemorrhage (DAH), namely rapidly progressive dyspnea, anemia, and hemoptysis (which can be absent). Tracheobronchial involvement can lead to subglottic stenosis, with secondary atelectasis and bronchopneumonia. The most characteristic CT-scan appearance in the lungs ^{6,7} consists of multiple nodules of variable size, frequently with a ground glass halo and with the tendency to cavitate due to progressive necrosis. Presentation as a solitary nodule is unusual ⁸. Other radiological features can be found, including bilateral ground glass opacities in patients with DAH. Kidney involvement is variable, with

rapid progression to renal failure in some patients. Eyes and orbits, oral mucosa, peripheral and central nervous system, skin, and joints are also affected, but GPA is a systemic disease and any site can be involved, sometimes with atypical and misleading clinical manifestations. Systemic symptoms are reported in the majority of the patients. Cases of GPA limited to one organ, including the lungs, are also described. Laboratory tests, particularly serology for anti-neutrophil cytoplasmic antibodies (ANCA) ^{9,10}, are important for diagnosis. Approximately 80% to 95% of ANCA found in GPA have a cytoplasmic pattern of immunofluorescence (c-ANCA) and are directed against proteinase 3. These antibodies have a specificity for GPA higher than 95% and a sensitivity that varies between 95% and 30%, depending on the extent of disease and activity.

MICROSCOPIC FEATURES

The wide clinical variability of the disease corresponds to an equally broad range of microscopic findings, particularly in the lung ^{5,11-19}. Following Colby's approach ¹⁴, a useful way to deal with the histologic complexity of GPA is to split out the pathologic changes into three components: vasculitis, necrotizing granuloma, and inflammatory background. In our experience, true vasculitis is much less common than the presence of granulomatous necrosis and inflammation.

Vasculitis in GPA may affect capillaries and small to medium-sized arteries and veins. It is morphologically variable (Fig. 1). It may consist of a focal, intimal, or

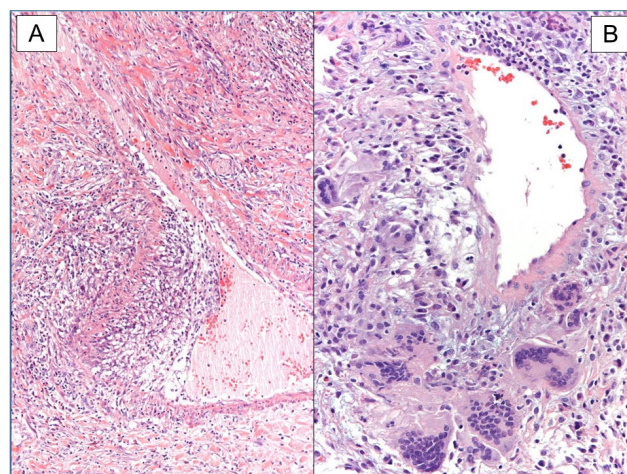


Figure 1. Vasculitis in GPA. In these two examples, trans-mural inflammation is focally necrotizing in A (hematoxylin-eosin, 40X) and granulomatous with giant cells in B (hematoxylin-eosin, 100X), two features typically found in GPA in extra-vascular parenchymal lesions as well.

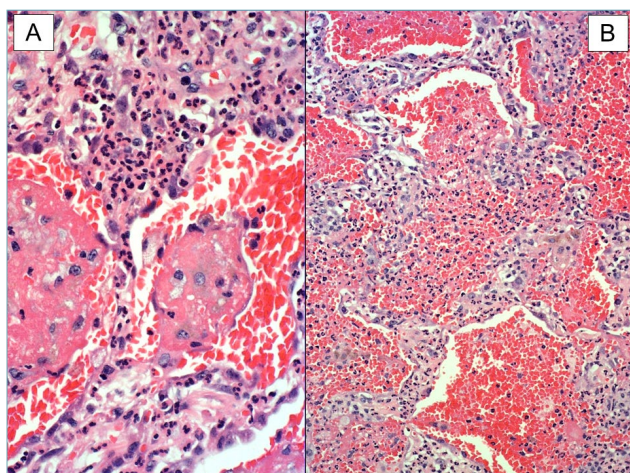


Figure 2. Capillaritis in GPA. Neutrophils in the alveolar septa associated with DAH, consisting of intra-alveolar blood red cells and fibrin (A, hematoxylin-eosin, 100X). When capillaritis is massive, neutrophils overflow into the alveolar lumen simulating an infectious pneumonia (B, hematoxylin-eosin 50X).

transmural mixed inflammatory infiltrate, sometimes with necrotizing features similar to those observed in the parenchyma (see below). The inflammation may be granulomatous or non-granulomatous. Over time, vasculitis may heal leaving chronic non-specific scarring. Vasculitis can be detected within inflammatory nodules but also in the uninvolved parenchyma.

In the lungs, a distinctive form of vasculitis is represented by capillaritis (Fig. 2), which consists of a predominantly neutrophilic inflammation of small vessels, with expansion and sometimes necrosis of the alveolar septa. Associated edema and reactive changes in the endothelium are often observed. When massive, neutrophils may extend into the alveolar lumen simulating an infectious acute lung injury. Capillaritis is the leukocytoclastic vasculitis of the lung and is associated with acute DAH. Capillaritis can be found in several immune-mediated vasculitic diseases in addition to GPA.

GPA is more than a vasculitis: it is a vasculitis *and* an aseptic necrotizing process. Particularly in small biopsies, vasculitis is infrequently sampled: it is important to emphasize that the histologic diagnosis of GPA can be suggested even without vasculitis when the biopsy shows the characteristic *parenchymal necrosis*. Necrosis in GPA is not ischemic. It starts as small foci of fibrinoid necrosis or, more commonly, as collections of neutrophils degenerating in small microabscesses (Fig. 3). Palisading histiocytes around the necrosis and scattered giant cells are frequently observed,

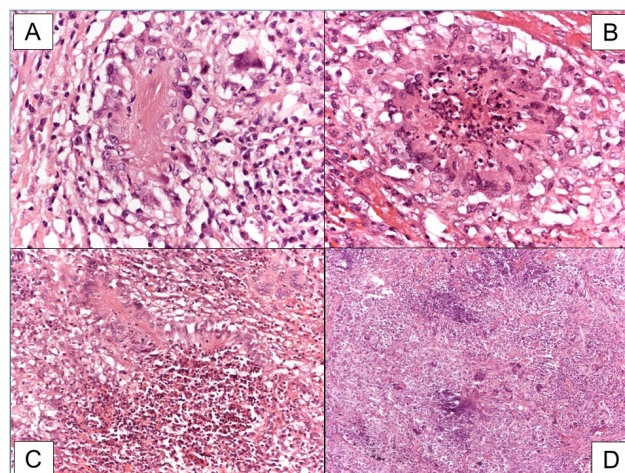


Figure 3. Early parenchymal necrosis in GPA consisting of small foci of fibrinoid necrosis (A, hematoxylin-eosin 200X), sometimes suppurating (B, hematoxylin-eosin 200X) or in microabscesses. Necrotic foci are frequently surrounded by palisading histiocytes. The wheel-like features shown here are almost pathognomonic of GPA (C, hematoxylin-eosin, 100X). Multiple microabscesses in an inflammatory background associated with scattered giant cells; notice the hyperchromatic nuclei of the giant cells, which allow their easy detection even at low magnification (D, hematoxylin-eosin 20X).

whereas well-formed granulomas are very unusual and their presence should suggest an alternative diagnosis. Giant cells in GPA are generally sparse but easily detected even at low magnification because their nuclei tend to be hyperchromatic. Over time, the necrotic foci expand and coalesce to form typical large areas of geographic basophilic necrosis (Fig. 4). Even in this advanced phase, small foci of incipient necrosis are frequently found in the surrounding lung.

Necrosis in GPA does not involve normal parenchyma but arises in a previously inflamed/abnormal tissue. This *inflammatory background* is morphologically variable: distinct backgrounds define different histological variants and clinical presentations. For example, the clinically acute phase may histologically correspond to DAH (Fig. 5)²⁰⁻²² characterized by endoalveolar accumulation of red blood cells and fibrin, sometimes strictly connected to capillaritis, hyaline membranes, organizing pneumonia and, pneumocyte hyperplasia. In the chronic phase, a generally mild interstitial fibrosis associated with a large accumulation of macrophages laden with hemosiderin pigment can be observed. The elastic lamina of vessels may become encrusted with iron and an associated giant cell reaction, improperly known as “endogenous pneumoconiosis,” may also occur. Some authors refer to this as iron en-

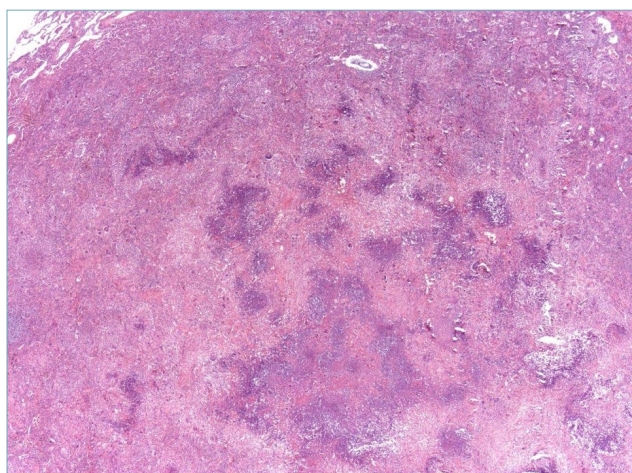


Figure 4. An inflammatory parenchymal nodule in GPA, with large areas of geographic basophilic necrosis arising from the enlargement and coalescence of multiple microabscesses (hematoxylin-eosin, 20X).

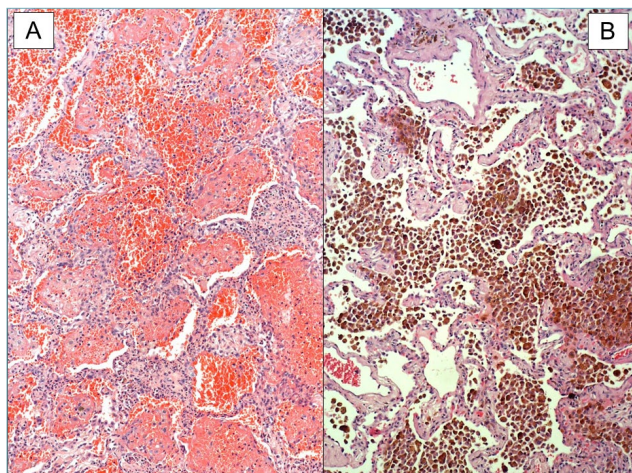


Figure 5. Acute DAH in GPA with intra-alveolar blood, fibrin, and capillaritis (A, hematoxylin-eosin 100X). Chronic DAH with many macrophages filled with coarse hemosiderin pigment and mild interstitial fibrosis (B, hematoxylin-eosin 100X).

crustation of arteries. In recurring pulmonary bleeding, foci of acute hemorrhage may be superimposed on a chronic background.

In some examples of GPA the background mostly consists of organizing pneumonia²³, whereas in others the inflammatory process tends to be broncho-bronchiolocentric with chondritis²⁴ (Fig. 6). Other cases may show an impressive ring of fibrin surrounding the areas of mixed inflammation. Occasionally eosin-

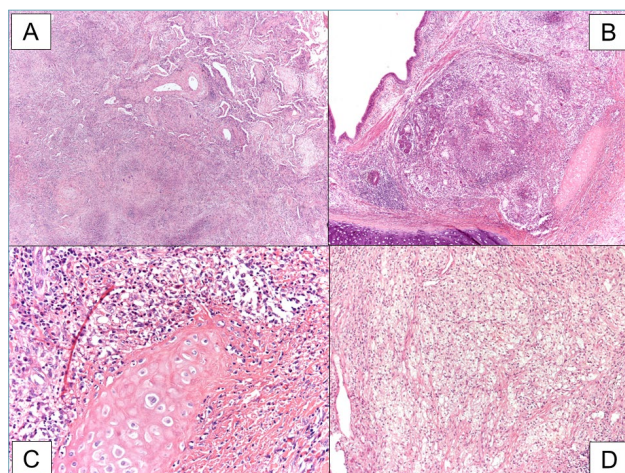


Figure 6. Examples of inflammatory background in GPA. Organizing pneumonia, with the characteristic serpiginous suppurative necrosis recognizable in the lower part of the picture (A, hematoxylin-eosin 20X). Involvement of the large bronchi (B, hematoxylin-eosin 20X) with chondritis (C, hematoxylin-eosin 100X); chondritis is a relatively frequent albeit nonspecific finding in GPA. Treated GPA, leaving a non-specific fibroinflammatory process rich in foamy histiocytes (D, hematoxylin-eosin 50X).

ophils can be numerous²⁵. A proportion of biopsies reveal a nonspecific increase in IgG4-positive plasma cells²⁶ (Fig. 7): The genuine coexistence of GPA with IgG4-related disease or other immune-mediated conditions including collagen vascular disease and inflammatory bowel disease²⁷ is rare. The inflammatory process may become fibrotic and sometimes rich in foamy histiocytes, both spontaneously or following therapy²⁸: in this phase of the disease the histological diagnosis may become impossible. The inflammatory background, although nonspecific, could often be so prevalent that overshadows the more characteristic necrosis and angiitis.

Eosinophilic granulomatosis with polyangiitis

Eosinophilic granulomatosis with polyangiitis (EGPA), formerly known as Churg-Strauss syndrome, is a rare systemic disorder mainly occurring in middle-aged adults, but with a wide age range. Clinically, allergic rhinitis, nasal polyps, and sinusitis, followed by asthma with blood and tissue eosinophilia characterize the early pre vasculitic phase of the disease. In the subsequent vasculitic phase, multiorgan involvement, fre-

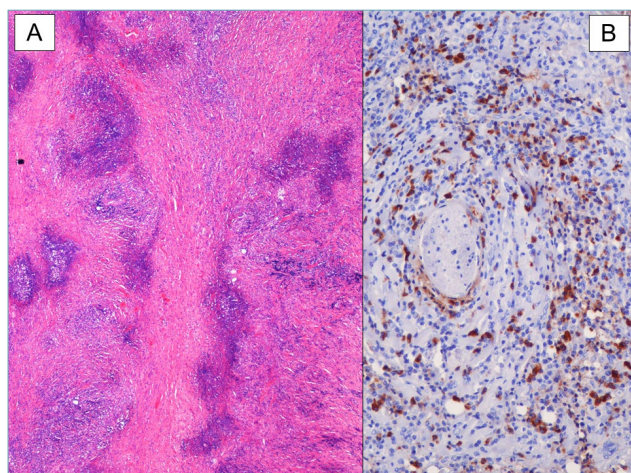


Figure 7. 33-year-old male presenting with a retroperitoneal mass, radiologically consistent with retroperitoneal fibrosis, with a serologic increase of both IgG4 and c-ANCA. A biopsy of the mass shows a fibro-inflammatory process with an area of irregular suppurative necrosis (A, hematoxylin-eosin 20X). Tissue IgG4-positive plasma cells are increased (B, peroxidase-antiperoxidase, 100X). This case was interpreted as GPA simulating retroperitoneal fibrosis.

quently cardiovascular, cutaneous, neurological, and pulmonary²⁹ may occur. Renal involvement is quite rare and mild compared to other ANCA-associated vasculitides. In the lung, the most frequent CT findings consist of multifocal parenchymal consolidations, ground-glass opacities, nodules, and thickening of interlobular septa and bronchial walls³⁰. Serum eosinophilia ($> 1.5 \times 10^9/L$ or $> 10\%$ depending on definitions) can fluctuate during any phase of the disease, does not correlate with its activity, and is rapidly suppressed by steroid therapy. ANCA, mostly with a perinuclear staining pattern (p-ANCA), are positive in about 40% of cases and are associated with an higher prevalence of the clinical manifestations of vasculitis (particularly renal disease and DAH) and with a lower prevalence of parenchymal eosinophilic infiltration (particularly eosinophilic pneumonia and eosinophilic myocarditis)³¹.

MICROSCOPIC FEATURES

The classical histological triad of EGPA consists of tissue eosinophilic infiltration, vasculitis, and necrotizing granulomas. In the lung^{11,32}, tissue eosinophilia manifests as eosinophilic pneumonia, consisting of intra-alveolar and interstitial eosinophils variably intermingled with fibrin, organizing pneumonia and intra-alveolar macrophages (Fig. 8). Eosinophils are typically numerous, but they tend to rapidly disap-

pear after steroid therapy. Alterations of the airways secondary to asthma, such as mucus plugs, thickening of basement membrane, and smooth muscle wall hyperplasia, are frequently observed. Vasculitis is characterized by a predominantly eosinophilic transmural infiltrate involving the small arteries and veins; fibrinoid necrosis may occur, and sometimes the inflamed vessels acquire granulomatous features with giant cells. Capillaritis with alveolar hemorrhage may be also seen, but it is rare. Necrotizing granulomas occur in the context of eosinophilic pneumonia and consist of eosinophilic microabscesses or necrotic foci, typically surrounded by palisading histiocytes, analogous to the finding of neutrophilic microabscess in GPA.

Unfortunately, it is very unusual to find the full spectrum of histologic changes described above in the majority of biopsies performed on EGPA patients, the only detectable lesion is represented by eosinophilic infiltrates, a non-specific finding that becomes significant only in the appropriate clinical setting. Tissue eosinophilia can be demonstrated not only in biopsies but also in cytological samples, mainly obtained by bronchoalveolar lavage. In general, an EGPA diagnosis cannot be made by histology or cytology alone and requires adequate clinical and laboratory data correlation. Indeed, the 2022 criteria for the diagnosis of EGPA involves only one pathologic finding (extravascular eosinophilic-predominant inflammation)

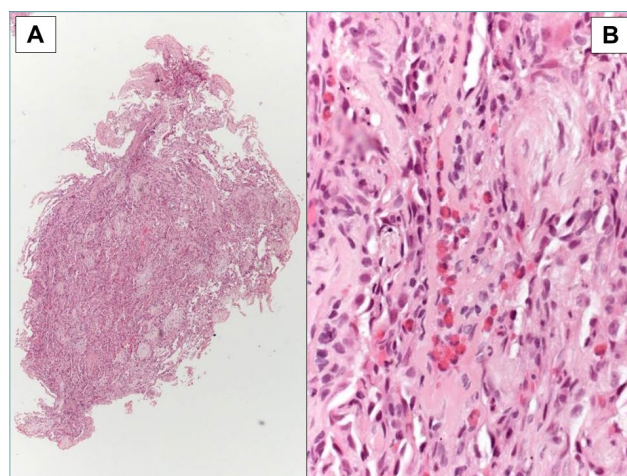


Figure 8. Transbronchial biopsy showing chronic eosinophilic pneumonia, consisting of eosinophilic infiltrate associated with organizing pneumonia, in a patient with EGPA (A, hematoxylin-eosin 40X; B, hematoxylin-eosin 200X). Like in this case, the majority of the biopsies in EGPA simply confirm tissue eosinophilia, and this information, per se non-specific, is integrated into the clinical diagnosis.

among six other clinical/laboratory findings (absolute eosinophil count, obstructive airway disease, nasal polyps, ANCA results, mononeuritis/neuropathy, and hematuria³³.

Microscopic polyangiitis

Microscopic polyangiitis (MPA)^{4,34} is a necrotizing vasculitis predominantly affecting small vessels (capillaries, arterioles, and venules); small and medium arteries may be involved as well. MPA is the most common cause of pulmonary-renal syndrome. Pulmonary involvement is observed in about half of patients, presenting with acute DAH or, more rarely, with a chronic subclinical course. In the majority of patients renal involvement occurs, frequently as acute renal failure. Cutaneous involvement, often represented by leukocytoclastic vasculitis-induced purpura, neurological manifestations with peripheral neuropathy, and musculoskeletal symptoms such as myalgia and arthralgia, are also frequent.

MICROSCOPIC FEATURES

Except the kidney, in which necrotizing glomerulonephritis with crescents is usually characteristic, the most common histological lesion observed in MPA is leukocytoclastic vasculitis, consisting of a predominantly neutrophilic inflammatory infiltrate of the capillaries with nuclear dust, variably associated with fibrinoid necrosis^{11,36}. Necrotizing vasculitis of arterioles, venules, and small and medium-sized arteries may coexist. Over time, the acute inflammatory infiltrate may disappear or may be replaced by a chronic lymphoplasmacytic component with scarring and leading to vascular thrombosis and obliteration.

DAH with or without capillaritis is the most frequent pulmonary lesion found in MPA. The capillaritis of MPA is indistinguishable from GPA or any other cases of capillaritis. As discussed before, capillaritis is a nonspecific finding and can be found in many different conditions presenting with DAH.

Other small vessel vasculitides

Although less frequent than the ANCA-associated, other small vessel vasculitides can involve the lung. *IgA vasculitis* (Henoch-Schönlein purpura) predominantly affects children and presents with skin purpura, arthralgia, abdominal pain, and hematuria. This clinical picture is due to systemic small vessel vasculitis caused by deposits of IgA in the vessel walls, recognizable by immunofluorescence analysis. Pulmonary

involvement is rare and consists of DAH with capillaritis³⁵.

Anti-glomerular basement membrane disease (Goodpasture's disease) is a rare condition that typically involves the kidney and the lungs. It is caused by antibodies directed against specific amino acid sequences of collagen IV, mainly exposed on the basement membranes of renal glomeruli and lung alveoli. The main symptoms, variable in severity, include hemoptysis, cough, dyspnea, fever, and hematuria. Lung involvement^{36,37} consists of acute DAH. Capillaritis may occur, but is usually less pronounced than in ANCA-associated vasculitides.

Similarly, *cryoglobulinemic vasculitides* can cause capillaritis with pulmonary hemorrhage due to cryoglobulin deposits in alveolar capillaries.

Vasculitis may occur in any *connective tissue disease*, but the phenomenon is rare except in systemic lupus erythematosus in which it generally presents as capillaritis with DAH.

A large number of drugs have been reported to cause vasculitis, mostly ANCA-associated small vessel vasculitis, although medium and large vessel vasculitis may occur as well³⁸. Pulmonary involvement generally manifests as capillaritis with DAH. An incomplete list of drugs reported to cause vasculitis is shown in Table I.

Medium and large vessel vasculitides

Occasionally, vasculitides affecting medium to large vessels can involve the lungs.

Takayasu arteritis is a vasculitis typically affecting women before the age of 50 years, involving the aorta and its branches, occasionally the pulmonary arteries. In the acute phase, histology (Fig. 9) shows giant cell arteritis with a transmural chronic inflammatory infiltrate with minimal or absent necrosis, leading to the destruction of the elastic lamina. Over time, the reparative fibrosing process of the arterial wall predisposes to aneurysm formation or thrombosis, the latter sometimes resulting in pulmonary hypertension.

Behçet disease^{40,41} is a systemic vasculitis that can involve vessels of any size and type. At histology, a chronic vasculitis without necrotizing nor granulomatous features are observed. Vasculitis is just one of the manifestations of the disease which includes recurrent oral and genital ulcers and cutaneous, ocular, joint, gastrointestinal, and neurological inflammatory lesions. Pulmonary involvement is infrequent and, over time, can lead to aneurysms of pulmonary arteries or thrombosis of smaller caliber arteries and veins, with secondary infarcts (Fig. 10).

Table I. Drugs reported to cause vasculitis.

Drug classification	Drug	Type of vasculitis
Anti-thyroid drugs	Benzylthiouracil, Carbimazole, Methimazole, Propylthiouracil	ANCA-associated vasculitis
Biological agents	Adalimumab, Etanercept, Infliximab, Golimumab	ANCA-associated vasculitis
Antibiotics	Cefotaxime, Minocycline, Nitrofurantoin, Trimethoprim-sulfamethoxazole, Vancomycin, Doxycycline	ANCA-associated vasculitis
Anti-tuberculosis drugs	Isoniazid, Rifampicin	ANCA-associated vasculitis
DMARDs	D-Penicillamine, Sulfasalazine	ANCA-associated vasculitis
Psychoactive agents	Clozapine, Thioridazine	ANCA-associated vasculitis
Miscellaneous drugs	Allopurinol, Atorvastatin, Cocaine (vasculitis attributed to levamisole that frequently contaminates cocaine) ³⁹ , Denosumab, Hydralazine, Isotretinoin, Phenytoin	ANCA-associated vasculitis
Vasodilator	Hydralazine	ANCA-associated vasculitis
Granulocyte colony-stimulating factor (G-CSF) drugs	lipegfilgrastim, lenograstim, filgrastim, pegfilgrastim	Large vessel vasculitis
Immune check point inhibitors	gemcitabine and immune checkpoint inhibitors (ICIs) such as monoclonal antibodies targeting PD-1	Large vessel vasculitis

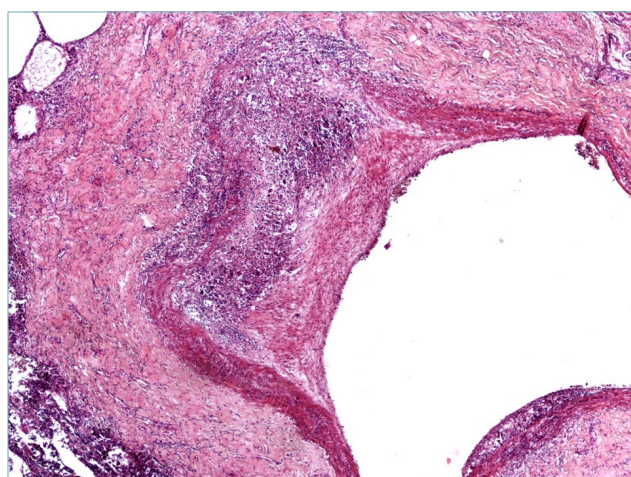


Figure 9. Takayasu arteritis in a 52-year-old woman with multiple aneurysms of the pulmonary artery at CT scan, leading to massive hemoptysis and death. At autopsy, a giant cell vasculitis of the branches of the pulmonary artery was found (case courtesy Prof. Camilla E. Comin, Florence) (hematoxylin-eosin, 50X).

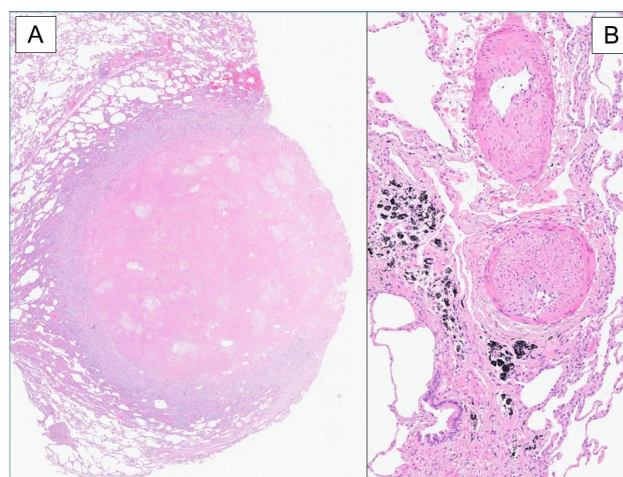


Figure 10. 33-year-old male affected by Behçet disease, presenting with bilateral pulmonary nodules at CT scan, consisting histologically of infarcts (A, hematoxylin-eosin 20X). In the surrounding pulmonary parenchyma, multiple chronic thromboses of the small arteries was found (B, hematoxylin-eosin 100X).

ANCA-associated vasculitis and fibrosing interstitial lung disease

Occasionally ANCA-associated vasculitis and fibrosing interstitial lung disease coexist in the same patient. Between 4-36% of patients with idiopathic interstitial lung diseases, mainly idiopathic pulmonary

fibrosis, are positive for ANCA, more frequently p-ANCA⁴². A proportion of these patients develop vasculitis, generally with the clinical features of MPA. More rarely, clinical onset of vasculitis precedes the diagnosis of interstitial lung disease, or they concurrently occur. There are many reports of fibrosing lung disease in the setting of ANCA-associated vasculitis.

Histologic differential diagnosis

Given the wide range of clinical and pathological presentations, the histological differential diagnosis of vasculitis is broad, and the lesions to be considered vary from case to case. This is particularly true for GPA: for this reason, this section is focused on GPA, but all vasculitides more frequently involving the lung are considered as well.

GPA VERSUS GRANULOMATOUS INFECTIONS

The most frequent diagnostic challenge in GPA is with infection^{5,14,19}. Although the classical histological features of GPA and infections are different (see below), whenever GPA is considered, it is wise to exclude infection through special stains and possibly cultures. If the suspicion of infection is high but the stains result negative, it may be helpful to repeat them on different tissue blocks or different sections from the same block. If the patient has a solitary lung lesion, a diagnosis of GPA should be approached cautiously. Despite being described⁸, this presentation is unusual in GPA and favors an infectious etiology. It should be noted that an opportunistic infection may complicate any vasculitis and the presence of microorganisms does not completely exclude the possibility of underlying GPA. The clinical presentation can be a helpful clue: patients with bilateral nodules and cavitary masses related to infection tend to be much more ill than those presenting with GPA.

The main histological criteria useful to differentiate GPA from granulomatous infections are listed in Table II.

While the presence of vasculitis favors GPA, inflammatory changes involving vessels are nonspecific and are also seen in infections-related inflammation (Fig. 11). A vasculitis localized in the normal parenchyma, away from the inflammatory mass, is more significant and favors GPA, but is quite unusual.

The characteristics of necrosis are frequently more important than vasculitis itself. Necrosis in infections generally consists of round, eosinophilic nodules, typically with a thinner inflammatory background com-

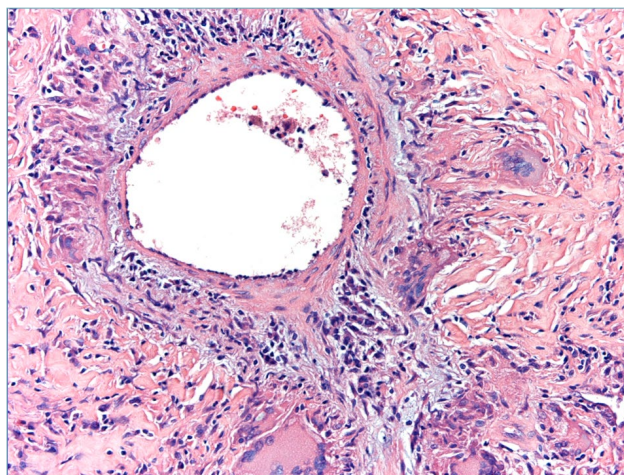


Figure 11. Granulomatous vasculitis due to mycobacteria infection. Vasculitis may occur as a nonspecific localized phenomenon whenever vessel walls are directly involved in an inflammatory process (hematoxylin-eosin, 100X).

pared to GPA. The scattered small suppurative foci typical of GPA are generally absent. Over time, necrosis in GPA may round up and become similar to an old granulomatous infection but, it usually retains its basophilic appearance.

Criteria also useful in differential diagnosis are the characteristics of the granulomas. The typical granulomas of infections are well-formed and necrotizing.

Finally, the frequency and morphology of the giant cells can be a clue to the diagnosis. Giant cells in GPA tend to be rare, smaller, hyperchromatic, and with fewer nuclei. In contrast, giant cells in infections are frequent, larger, hypochromatic, and have abundant nuclei.

GPA VERSUS OTHER VASCULITIDES PRESENTING WITH DAH

The presence of blood in a lung biopsy of any type is very frequent, and in most cases it is an artefact due to trauma from the biopsy procedure. Histologic clues suggesting that bleeding is real are capillaritis and a tissue reaction to blood like fibrin, organizing pneumo-

Table II. Main histologic criteria useful in the differential diagnosis between GPA and granulomatous infections (modified from reference n. 5).

	GPA	Granulomatous infections
Vasculitis	+/-	-/+
Necrosis	Multiple foci of collagen necrosis and/or microabscesses, geographic areas of basophilic necrosis within a large inflammatory background	Round nodules of eosinophilic necrosis with a thinner inflammatory rim
Granulomatous inflammation	Palisading histiocytes around necrosis, scattered giant cells	Well formed granulomas, frequently necrotizing
Giant Cells	Rare, smaller, darker chromatin, fewer nuclei	Frequent, larger, lighter chromatin, more nuclei

Table III. Main causes of alveolar hemorrhage.

Vasculitides	GPA, MPA, EGPA, cryoglobulinemia, IgA vasculitis, anti-glomerular basement membrane disease, drugs including cocaine, etc.
Collagen vascular diseases	Lupus (mainly)
Tumors involving diffusely the lung	Angiosarcoma (primary and metastatic), lymphangioleiomyomatosis, etc.
Infections	Any micro-organisms, particularly in the immunosuppressed patient
Miscellaneous conditions	Coagulopathies, heart failure, pulmonary hypertension, amyloidosis, pulmonary and bone marrow transplantation, idiopathic pulmonary hemosiderosis and other idiopathic conditions, etc.

nia and hemosiderin, but occasionally the correct interpretation requires input from the clinician. Genuine pulmonary bleeding can be secondary to a localized lesion (including infections, tumors, vascular malformations, bronchiectasis, and chronic bronchitis), or can be diffuse (DAH) ^{21,22}. The main diseases which can cause alveolar hemorrhage are listed in Table III. The histology of DAH due to vasculitis is characteristic (Fig. 5) and does not depend on the specific vasculitis, except for GPA and EGPA, which in addition to hemorrhage may show the characteristic features previously described. When the latter are absent, the histological features are undistinguishable from those of other vasculitides. Moreover, in the setting of DAH due to ANCA-associated vasculitis, the treatment is generally the same regardless of the specific disease. For these reasons, in the vast majority of the patients with DAH, diagnosis and treatment are based on clinic-radiologic and serologic data, sometimes coupled with BAL, and biopsy is not usually required.

GPA VERSUS MISCELLANEOUS CONDITIONS

The inflammatory background of GPA can simulate different conditions, including organizing pneumonia and nonspecific inflammatory processes. When eosinophils are present in a significant number, GPA should be distinguished from EGPA: the distinction is mostly based on clinical data.

Rheumatoid nodules may simulate the necrotic lesions of GPA. A rich inflammatory background with multiple foci of suppurative necrosis, scattered giant cells, and vasculitis in the uninvolved parenchyma favor GPA, whereas a septal/pleural localization and the presence of features suggesting a connective tissue disease in the surrounding lung (cellular/follicular bronchiolitis, lymphocytic interstitial infiltrate, many plasma cells, pleuritis etc.) favor a rheumatoid nodule. Clinical information is mandatory.

Other aseptic necro-inflammatory conditions like Sweet syndrome ⁴⁵, pyoderma gangrenosum ⁴⁶, and inflammatory bowel diseases ⁴⁷ rarely involve the lung, and the differential diagnosis with GPA can be very difficult without clinical information.

Particularly in small biopsies the distinction with lym-

phoma is occasionally difficult, but it can be easily supported by immunohistochemical stains.

The role of the pathologist

Clinical, laboratory, and radiographic data are usually adequate for a firm diagnosis of vasculitis for treatment decisions. Biopsy or cytologic samples are required only in a proportion of cases and the pathological data can be crucial for the correct management of the patient.

When involved, the pathologist is faced with one of the following clinical scenarios:

- The possibility of vasculitis has not been considered by the clinician, because the clinical presentation is atypical (Fig. 12) or for any other reason. In this setting, the task of the pathologist is to think about the possibility of vasculitis and to suggest such a hypothesis to the clinician. It is never wise to make this diagnosis based on morphologic findings only, although raising this possibility is generally sufficient to induce the appropriate clinical workup. For the pathologist, this scenario is in the meantime an opportunity and a risk: the opportunity is to be the first to suggest the diagnosis of vasculitis, with a potentially huge impact on the patient; the risk is to miss this opportunity.
- The possibility of vasculitis has been considered by the clinician. In this setting, the task for the pathologist is to correctly modulate the probability of this diagnosis or to suggest alternative diagnostic possibilities (Fig. 13).
- The patient is affected by a known vasculitis for which he/she has been treated and presents with acute/subacute pulmonary symptoms and with new alveolar opacities at a CT chest scan. In this setting, the main diagnostic considerations are opportunistic infection, drug reaction, and recurrence of vasculitis. The task for the pathologist is to help in this differential diagnosis, and particularly to exclude infection. Minimally invasive diagnostic procedures like BAL are frequently informative in these cases.

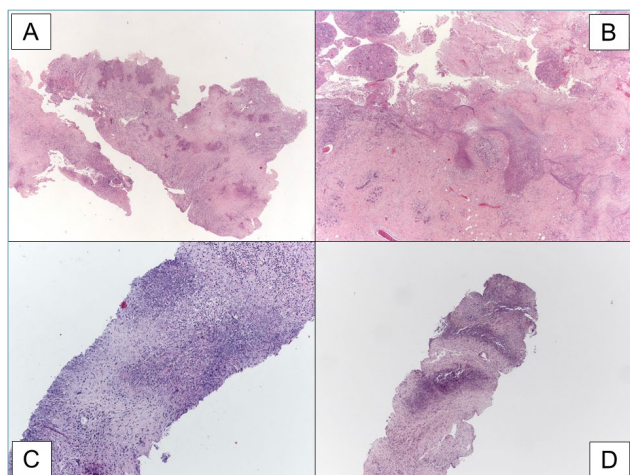


Figure 12. Examples of GPA with atypical clinical presentation, in which the diagnosis was raised initially by the pathologist. Meningeal biopsy in a patient presenting clinically with meningitis (A, hematoxylin-eosin 20X), quadrantectomy for a breast mass (B, hematoxylin-eosin 40X), kidney biopsy for a renal nodule (C, hematoxylin-eosin 40X) and prostatic biopsy in a patient presenting with prostatitis (D, hematoxylin-eosin 40X). In all these cases the pathologist valued the characteristic necrotic lesions and suggested the possibility of GPA. The diagnoses were subsequently confirmed clinically.

To accomplish these tasks, the pathologist has to be competent in the histologic complexity of vasculitis and its mimicry involving the lung. The quality of the communication and the mutual trust between pathologist and clinician are essential.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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AUTHORS' CONTRIBUTIONS

Study design: AC, PG. Reviewed the literature and wrote the manuscript: EA, AC. Data analysis: EA, AC, MLS, PG. Data interpretation: EA, AC. Manuscript review: AC, MLS, PG.

ETHICAL CONSIDERATION

Not applicable.

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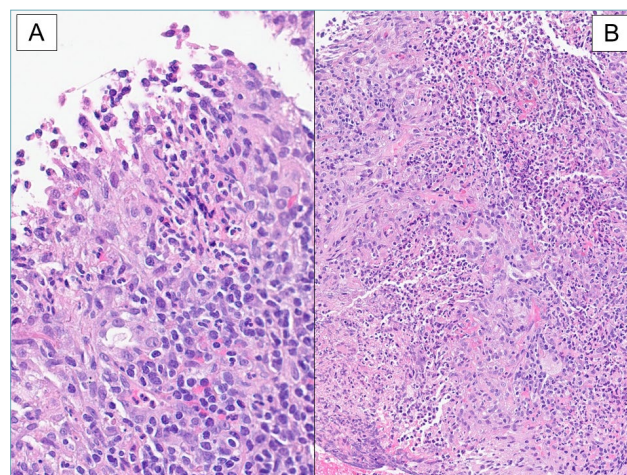


Figure 13. Examples of transbronchial biopsies in patients with clinical suspicion of GPA. In A the biopsy consists mostly of a nonspecific lympho-histiocytic inflammatory infiltrate, with only one small focus of neutrophils aggregate. This finding is consistent with GPA, but is very subtle and the level of diagnostic confidence is low (A, hematoxylin-eosin 250X). A different patient is illustrated in B, with a biopsy showing large, irregular suppurative areas with vague palisading histiocytes and a few giant cells, with nuclei not particularly hyperchromatic. Special stains for micro-organisms are negative. Also, this finding is consistent with GPA, but the level of diagnostic confidence is quite high (B, hematoxylin-eosin 150X). Not only the diagnostic hypothesis, but also the level of confidence, should be communicated to the clinician, as both become elements of the multidisciplinary discussion. In both patients the final diagnosis was GPA, but the contribution of histology was different.

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