Pulmonary-renal syndrome associated with antineutrophil cytoplasmic antibodies

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Abstract

Pulmonary-renal syndrome is defined by the association of alveolar hemorrhage and rapidly progressive glomerulonephritis (RPGN) resulting from various diseases, and frequently associated with serum positivity for antineutrophil cytoplasmic antibodies (ANCA). Wegener's granulomatosis (WG), microscopic polyangiitis and Churg-Strauss syndrome are described as small vessel vasculitis strongly associated with ANCA. Pulmonary-renal syndrome is the most common clinical manifestation of systemic vasculitis. The diagnosis of ANCA-associated vasculitis is made based on clinical manifestations, biopsy of the affected organ, and the serum presence of ANCA. However, the use of ANCA testing as a tool for clinical diagnosis is still regarded as controversial. An accurate understanding of the key pathogenic points of ANCA-associated vasculitis can undoubtedly provide a more rational therapeutic approach.

Key words: ANCA, vasculitis, Wegener's granulomatosis, microscopic polyangiitis, Churg-Strauss syndrome.

Pulmonary renal syndrome includes the group of vasculitis mainly involving the small vessels (*Table I*; classification of vasculitis, according to the International Chapel Hill Conference, based on vessel caliber).[1] This syndrome is of unknown etiology; there are no immune deposits in the blood vessels, and ANCA (antineutrophil cytoplasmic antibody) is involved in the respective pathogenesis.

ANCAs are predominantly IgG antibodies, directed against granular components of the neutrophil and lysosomes of the monocyte and are associated with primary systemic vasculitis.[2]

Vasculitis (inflammation and necrosis of the walls of the blood vessels) is classified by origin (infectious or non-infectious) or its association with basement disease (primary vasculitis or idiopathic and secondary vasculitis); it can take different forms of expression, ranging from a local auto limited inflammatory process, to a form with widespread and extremely severe involvement (isolated or systemic form).[1]

Wegener's Granulomatosis (WG), microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS) are described as strongly ANCA-associated small vessel vasculites. Given the low prevalence of these vasculites in the general population (20-100 cases per million) and the multi-syndromatic presentation, diagnosis is difficult, even for specialists with vast experience in this area.[3]

Discovery and theories about the genesis of ANCA

ANCA was discovered in 1982, when Davies and colleagues evaluated the presence of antinuclear antibodies (ANA) in the serum of patients with segmentary necrotic glomerulonephritis. Later (1985), this antibody was also identified in patients with WG. Animal experiments confirmed the pathogenic role of this antibody, and since then, the presence of ANCA has completed the diagnostic puzzle.

The etiological factors of ANCA-associated diseases remain unknown, but there are currently various theories on the formation of ANCA, the correlation between title and activity of the disease, and the role of ANCA in clinical manifestations.

In primary vasculitis, two major antigens for ANCA were recognized: proteinase 3 (PR3) and myeloperoxidase (MPO). MPO is found exclusively in the azurophilic granules, while PR3 is also found in the secretory vesicles.[2]

Other antigens involved in the formation of ANCA

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have been discovered: bactericidal/permeability-increasing protein (BPI), cathepsin G, elastase, lactoferrin, and lysozyme.

ANCA-associated vasculitis is more prevalent in the Caucasian population, which suggests the existence of a genetic base. In fact, immunospecific genes have been described that contribute to the development of ANCA and this type of vasculitis. The polymorphism of some CD18 alleles has been associated with MPO-ANCA vasculitis. Many researchers have looked for a link between HLA (human leukocyte antigens) and the development of vasculitis. Recent studies have reported a positive link between HLA DR1, DQw7 or DR8 and a negative association with DR13 or DR3.[4] Genes that codify cytokines, adhesion molecules, and protease inhibitors may also contribute to the development of this type of vasculitis.[5]

An association has been reported between PR3-ANCA and α1-antitrypsin deficit (physiological PR3 inhibitor) and the presence of the PI*Z allele has been observed as a risk factor for PR3-ANCA associated vasculitis.[6]

In the autoimmune response, some environmental factors have an inductive role, notably, exposure to silica, vaccination, infections, and certain drugs *(Table II)*.[3]

Two recent theories are considered important in the pathogenesis: the role of microbial superantigens, and apoptosis defects.[2]

1. Superantigens derived from bacteria, viruses and parasites are potent immune response stimulators, and can attract the B cells directly (independent response of the T-cells) for the production of antibodies such as ANCA. The *Staphylococcus aureus* toxins are superantigens with higher potency. In WG, 60-70% of patients are chronic carriers of *Staphylococcus aureus* in the nasal cavity; the possible role of *Staphylococcus* in this disease was suggested by the reported benefit of antibodies in this disease (sulfamethoxazole and trimethoprim).

2. Apoptosis of the neutrophils is the key mechanism in the control of the inflammatory response and limitation of tissue lesion caused by the neutrophil. Apoptosis defects and the removal of apoptotic cells result in constant stimulation of the immune system and permanent induction of the humoral response. The ANCA interacts with the granules on the surface of the apoptotic neutrophil (possible role of formation of an autoantigen during apoptosis).

TABLE I

International Nomenclature of Systemic Vasculitis 1993[1]

Vessel Caliber	Nosological entity
Large vessel vasculitis	Temporary arthritis (giant cells) Takayasu arthritis
Medium caliber vasculitis	Classical nodulous polyarthritis Kawasaki disease
Small vessel vasculitis	Wegener's granulomatosis* Microscopic polyangiitis* Churg-Strauss syndrome* Essential crioglobulinemia Henoch-Schönlein purpura Cutaneous leucocytoclastic vasculitis

*Closely ANCA-associated vasculitis

TABLE II

Environmental factors which induce ANCA[3]

Drugs	Infections
Propylthiouracil	Tuberculosis
Hydralazine	HIV/AIDS
Methimazole	Malaria
Minocycline	Hepatitis C
Carbimazole	Subacute endocarditis by *S. aureus* or *Strept.*
Alopurinol	Parvovirus B 19
Cocaine	Lepra
D-penicillamine	Pseudomonas (cystic fibrosis)
Phentoine	Aspergillosis
Levamisole	Histoplasmosis
Pimagedine	Leptospirosis
	Amebiasis
	Pulmonary Sporotrichosis

Pathogenic role of ANCA

The possible mechanisms of vascular lesion by ANCA are:

• Activation of the neutrophils and lesion of the mediated-neutrophil tissues, with the formation of oxygen and nitrogen free radicals, proteolytic enzymes and cytokines (TGF-β, TNF-α, IL-1).

• ANCA/neutrophil+endothelial cell (EC) interaction: adhesion, direct lesion and induction of cytokine

TABLE III

Table III. Clinical manifestations suggestive of vasculitis and guidelines of the Consensus for ANCA study[7]

1. Diffuse alveolar hemorrhage (DAH) with the classic diagnostic triad: diffuse alveolar infiltrates, hemoptysis (not always present), and drop in hemoglobin and hematocrit levels. Complementary methods of confirming this diagnostic: carbon monoxide diffusion (>30%), broncoscopy and bronco-alveolar washing, transbronchial and transthoracic biopsy.
2. Rapidly progressive glomerulonephritis (RPGN), identified by active urinary sediment (hematuria, dysmorphic erythrocytes, proteinuria >500 mg/dl) and high urea and creatinine levels. Clinically, edemas and hypertension are present.
3. Cutaneous vasculitis (with palpable purpura, myalgias, arthralgias or arthritis)
4. Nodular or cavitated pulmonary image.
5. Nasal disease; congestion, epistaxis, erosive alterations of the nasal mucosa, nasal septum perforation.
6. Sinusitis and/or chronic otitis.
7. Subglottic stenosis (alterations in voice, dyspnea, cough)
8. Mononeuritis multiplex or other peripheral neuropathy.
9. Retroorbital mass.

production by EC (IL-8).

• Activation of the macrophages by ANCA, with release of cytokines and growth factors.

• It was recently reported that PR3 and MPO induce proliferation of the T-cells CD4+ in ANCA positive patients.

In this context, immunopathological studies have demonstrated that in various vasculitic syndromes, the inflammatory infiltrate is comprised mainly of activated T-lymphocytes and macrophages.

The clinical manifestations that suggest vasculitis are summarized in *Table III*.[7]

Specific nosological entities

Wegener's Granulomatosis

This is a granulomatous inflammation that affects the respiratory system, with necrosing vasculitis of the small and medium caliber vessels capillaries, venules, arterioles and arteries). Necrosing glomerulonephritis is frequent (Chapel Hill Consensus Definition, 1994).

The disease was discovered and described in 1936, by Friedreich Wegener. It is characterized by the clinical triad of involvement of the upper respiratory airways (e.g. sinusitis, otitis, ulcerations, subglottic or bronchial stenosis), of the lower respiratory airways (e.g. chest pain, hemoptyses, dyspnea) and renal involvement (glomerulonephritis).[8] In the initial presentation of the disease, renal involvement may be absent (limited form); the lung is the organ most affected, with very aggressive pulmonary pathology, but as the disease progresses, 80-90% of patients develop renal pathology *(Table IV)*.[7,9,10,11,12] It is known that the life expectancy of patients with the generalized form is lower, compared with patients with the limited form. The diagnosis can take 4.7 to 15 months, on average,[9] which obviously influences the prognosis, given that without treatment, the majority of patients do not survive for more than one year.

To establish the diagnosis, two of the four following criteria must be present: mouth ulcers or runny nose; presence of nodules, fixed infiltrates or cavitations in the chest radiography; nephritic urinary sediment; and granulomatous infiltration in the biopsy (Criteria of the American College of Rheumatology, proposed before the ANCA test became available).[11]

Microscopic polyangiitis

Microscopic polyangiitis is a necrosing vasculitis which is characterized by the absence or lack of immune deposits, and which affects the small vessels (capillaries, venules, arterioles). Necrosing arthritis of the small and medium caliber arteries may also be present. Necrosing glomerulonephritis is very common, and pulmonary capillaritis occurs frequently (Chapel Hill Consensus Definition,1994).

Within the group of diseases known as polyarthritis nodosa (PAN), the nosological entity designated microscopic polyangiitis (MPA) was described for the first time by Wohlwill, and subsequently characterized by Davson. MPA was initially recognized as a particular subtype of PAN, with RPGN, and frequently, pulmonary hemorrhage. Currently, PAN is distinguished from MPA by the absence (versus presence) of vasculitis of the arterioles, venules, and capillaries. The involvement of the small vessels, when it is present, is a definitive criterion for MPA and excludes

TABLE IV

Clinical manifestations of WG[7,9,10,11,12]

Involvement of the organ or system	Frequent	Clinical
Pulmonary	70-95%	Cough, chest pain, dyspnea, hemoptysis
Renal	50-90%	RPGN
Oral lesions	6-13%	Hyperplasic gingivitis
Upper respiratory airways	70-90%	Sinusitis, ulcers and destructive lesions
General symptoms	Frequent	Fatigue, fever, weight loss
Musculoskeletal	50%	Arthralgias, arthritis, myalgias
Ocular	25-59%	Uveitis, eye ulcers
Cardiac	Infrequent	
Gastrointestinal	Infrequent	
Dermatological	Frequent	Palpable Purpura, ulcers, nodules and vesicles
Neurological	May be present	Involvement of the SNC or peripheral
Thoracic imagiology	>80%	Infiltrate, nodule, cavitation
ANCA	>90%	Majority cANCA positive (>85%).

PAN. The designation "Microscopic PAN" is currently considered to be synonymous with MPA.[13]

From the clinical point of view, it often has a prolonged prodromic phase (months and years), characterized by constitutional symptoms, followed by the development of RPGN *(Table V)*,[7,14,15,16] which justifies the difficulty in recognizing MPA. The interval between the onset of the disease and definitive diagnosis is, on average, 24 months for MPA and 17 months for PAN.[15] According to Loïc Guillevin, in the presence of inexplicable and non-specific signs and symptoms, a laboratory study of systemic vasculitis should be initiated, which includes urinary sediment (hematuria and proteinuria), ANCA dosing, and muscle biopsy to detect vasculitic lesions.[15]

RPGN is an almost universal condition, and pulmonary involvement occurs in a minority of patients (10-30%). However, when it does occur it is severe, the most common manifestations being pulmonary hemorrhage and capillaritis.

The incidence is 1:100000, with a slight predominance of males (ratio 1.24) and an average age at start of symptoms of 50 years.[13] ANCA is a useful diagnostic marker in cases of suspected MPA. The presence of ANCA and the absence of microaneurysms and/or stenosis should be used as diagnostic criteria for MPA. Thus, the immunological and angiographic findings, as a complement to the characteristic clinical condition, can help establish the correct diagnosis. MPA relapses are more frequent than those of PAN, observed in 7% of cases, and those of CSS, which occur in 23.8% of patients (Guillevin L et al)[13]. Some authors believe relapses are either of the same intensity or less severe than the initial presentation of the disease. The number of relapses is not correlated to mortality. Prognosis of the untreated disease is very reserved; the majority of patients will die within two years.[17]

Churg-Strauss syndrome

This syndrome is characterized by granulomatous eosinophilic inflammation of the respiratory airways and necrosing vasculitis which affects the small and medium caliber vessels, associated with asthma and eosinophilia (Chapel Hill Consensus Definition, 1994).

Initially described as allergic or angeitic granulomatosis more than fifty years ago, by two pathologists - Jacob Churg and Lotte Strauss[18] – it is characterized by the classic triad of asthma, hypereosinophilia and necrotizing vasculitis.[19,20] Although pulmonary hemorrhage and RPGN may occur, these conditions are less frequent than in other small vessel vasculitis.

Lanham describes three separate sequential phases in the progression of the disease: [(cit. in 21)] prodromic, eosinophilic and vasculitic. The prodromal phase is characterized by delayed onset - generally in the second and third decades of life - of atopic disease (allergic rhinitis, sinusitis, allergy to drugs and asthma) in patients without any family history of atopia.

TABLE V

Clinical manifestations characteristic of MPA[7,14,15,16]

Involvement of the organ or system	Frequency	Clinical
Pulmonary	10-30%	Alveolar/capillary hemorrhage
Renal	97%	RPGN
Upper respiratory airways	Variable	Chronic sinusitis
General symptoms	Frequent and precede RPGN	Fever, weight loss, tiredness
Cardiac	10-20% 35-45%	Abnormal ECG, systolic and/or diastolic dysfunction
Gastrointestinal	50%	Abdominal pain, hemorrhage, infarction, perforation, visceral aneurysm
Musculoskeletal	0-30%	Arthralgias, myalgias
Ocular	Frequent	Uveitis, eye ulcers
Dermatological	10-50%	Palpable purpura
Neurological	10-30%	Mononeuritis multiplex
Chest imagiology	50-75%	Pulmonary infiltrates, consolidation, standard in ground-glass
ANCA		Majority pANCA positive

The eosinophilic phase is characterized by hypereosinophilia in the peripheral blood (5000-9000/µl) and by the infiltration of eosinophils of multiple organs, particularly the lungs, digestive tube and skin. In the third and fourth decades of life, systemic vasculitis phase occurs, involving the small and medium caliber vessels, and is frequently associated with vascular and extravascular granulomatosis. Generally CSS forms part of the differential diagnosis of other pulmonary eosinophilic diseases: pneumonia, allergic broncopulmonary mycosis, drug reactions, hypereosinophilic syndrome, parasite infection, and of course, asthma.[21]

It must also be excluded (attention!) in asthmatic/atopic patients who develop a severe gastrointestinal disease (perforation, ischemia, hemorrhage) or cardiac disease (alterations in conduction, systolic or diasystolic dysfunction) (*Table VI*).[7,18,19,21]

It is observed that the clinical presentation of CSS is different from that of WG and MPA, described above.

To establish the diagnosis, 4 of the following 6 criteria must be present: asthma, perinasal sinus disease, peripheral eosinophilia >10%, mono or polyneuropathy, radiological evidence of transitory or migratory pulmonary opacities, and histological evidence of accumulation of eosinophils in extravascular areas (Criteria of the American College of Rheumatology).[22]

Complementary diagnostic exams

1. Imagiology: The chest radiography shows nodules or masses, cavitations (WG), and a diffuse interstitial or nodular pattern (CSS).

The chest CT shows nodules, masses, whether cavitated or not, parenchymatous consolidation, thickening or dilation of the bronchial walls at the segmentary or subsegmentary level, interlobular septal thickening, ground-glass attenuations, bronchiectasias, alterations in the tracheal wall, pleural irregularities and effusions, and hilar and mediastinal lymphadenopathy. In CSS, the cavitated nodular pulmonary lesions are very marked.[7,9,23] In one third of patients with CSS, there is evidence of pleural and pericardiac effusion in the CT.[21]

2. Evaluation of pulmonary function reveals obstructive ventilatory alterations in patients with CSS and in patients with WG. Central obstruction of the respiratory airways occurs in subglottic stenosis.

3. Bronchoscope and bronco-alveolar washing are characteristics of each syndrome: neutrophilic alveolitis in WG, eosinophilic alveolitis in CSS and macrophages with hemosiderin content in all forms, when pulmonary hemorrhage occurs.

4. Biopsy is the central exam in the diagnostic process: surgical lung or transbronchial biopsy, renal biopsy, biopsy of the respiratory airways, of the skin, muscle (necrosing vasculitis, necrotic granulomas characteristic of WG; vasculitis of the giant cells, eosinophilic vasculitis, tissue infiltration by eosinophils, extravascular granulomas with giant cells, and

TABLE VI

Clinical manifestations characteristic of CSS[7,18,19,21]

Involvement of the organ or system	Frequency	Clinical
Pulmonary	>95%	Asthma, generally severe, rapidly corticodependant; alveolar hemorrhage
Renal	10-50%	RPGN
Upper respiratory airways	20-70%	Chronic sinusitis
General symptom	Frequent	Fatigue, fever, weight loss
Cardiac	30-50%	Delayed conduction, myocarditis, eosinophil, coronary eosinophilic arthritis, coronary arthritis, dilated myocardiopathy; ischemic cardiopathy; acute or constructive pericarditis (without buffer)
Gastrointestinal	30-60%	Eosinophilic gastrenterocolitis, hemorrhages, abdominal pain, abdominal pain, perforation (intestinal vasculitis)
Musculoskeletal	50%	Arthralgias, myalgias, non-erosive myalgias
Ocular	Infrequent	
Dermatological	50-70%	Purpura, subcutaneous nodules, urticaria
Neurological	>50%	Mononeuritis multiplex; optical neuritis; subarachnoidal hemorrhage; cerebral effusion
Thoracic imagiology	40-75%	Normal; diffuse interstitial or nodular pattern
ANCA	45-70%	Majority pANCA positive

histiocytes characteristic of CSS.[8,12,21]

It is important to emphasize that the absence of characteristic alterations does not exclude the diagnosis, in the presence of strong suspicion.[9]

5. Laboratory Tests: Study of ANCA *(TableVII)*,[3] viral serologies, study of renal and hepatic function and a more specific study, depending on the clinical presentation. The study of circulating antiglomerular basement membrane antibodies is important for differential diagnosis with Goodpasture Syndrome.

There are some questions relating to the study and interpretation of ANCA which need to be taken into consideration:[24,25]

• The diversity of target antigens of ANCA;

The lack of standardization of the essays and their performance;

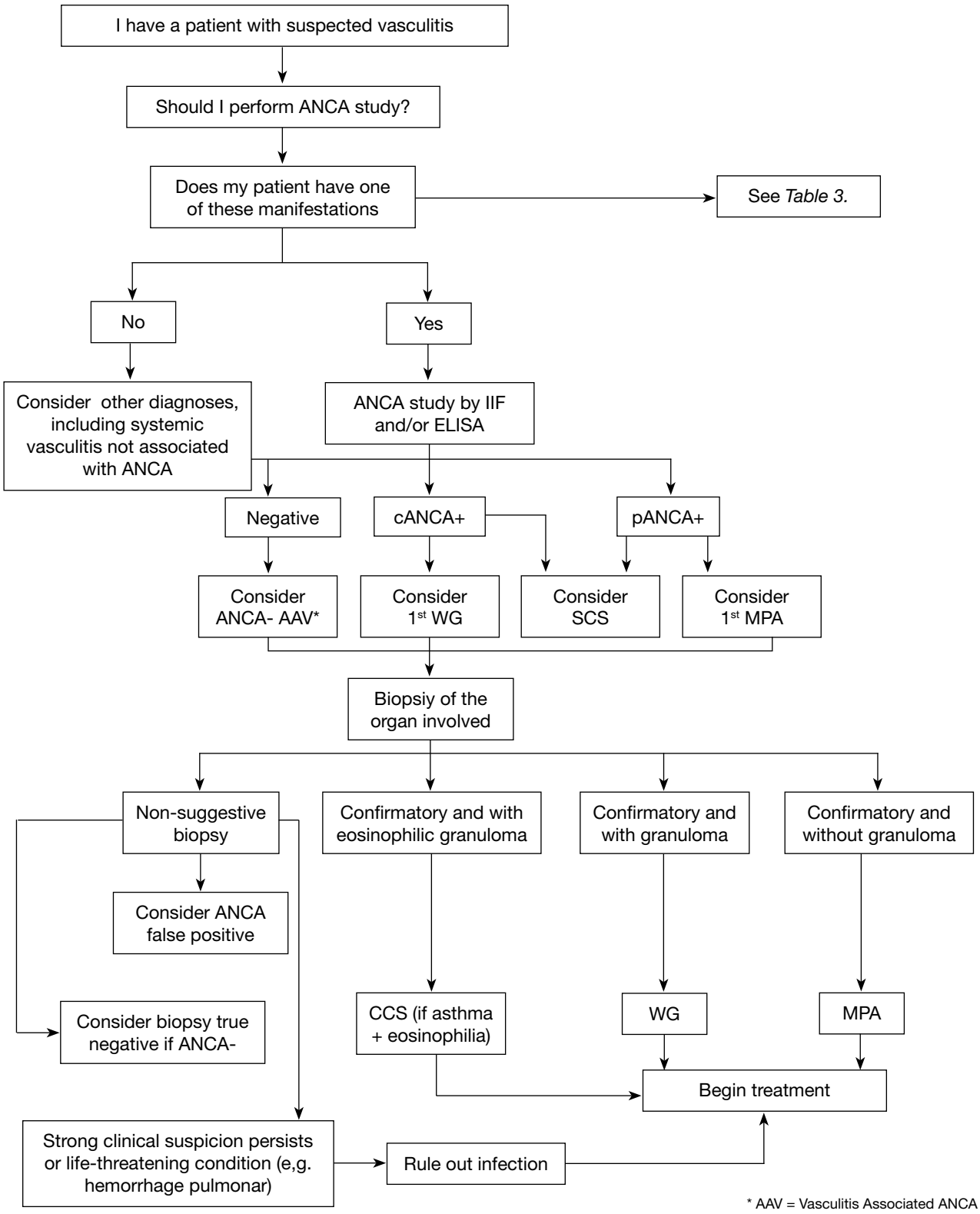
• The uses of ANCA tests in clinical contexts with low probability of ANCA-associated vasculitis;

• The widespread idea that the ANCA titles faithfully reflect the activity of the disease and that that they can be used as a guide to therapy.

To increase the sensitivity and specificity of the results, consensus guidelines were produced for the ANCA study tests *(Table III)*: the combined use of IFI (Indirect Immunofluorescence) and EIA (Immuno-Enzymatic Assay) for the MPO and PR3 specificities increases the PPV (positive predictive value) of ANCA from 59% to 79%.[26] The main problem with the use of ANCA assays is that there are still no international standards, therefore no standardization of titles has been determined;[27] the evolution of the ANCA titles of a given patient should always been performed by the same laboratory, using the same technique.

The request for ANCA tests should be restricted to clinical cases where there is a high level of suspicion *(Table III)*, in order to decrease the percentage of false positive results without running the risk of underdiagnosis. Certain clinical situations which are known to be associated with ANCA, regardless of the presence of vasculitis, should be carefully excluded, *(Table II)*, such as exposure to certain drugs and infections (particularly tuberculosis).

The therapeutic decisions and monitoring of the disease should not be based only on the results of the ANCA and on its variations in concentration, since there have been no sufficiently reliable studies to indicate this. However, a rapid increase in ANCA titles, or their reappearance after a period of negativity, should alert to the possibility of a relapse, and in these cases, other diagnostic approaches, or increased medical vigilance, are recommended.[28]



Value of ANCA assay in the diagnosis of systemic vasculitis.

FIG. 1

TABLE VII

Therapeutic induction options[7]

Classification	General symptoms	Renal function (creatinine)	Organ dysfunction	Induction option
Limited	No	<1.4 mg/dl	No	Corticosteroids or Methotrexate or Azathioprine
Generalized early	Yes	<1.4 mg/dl	No	Cyclophosphamide + Corticosteroid or Methotrexate + Corticosteroid
Generalized active	Yes	<5.7 mg/dl	Yes	Cyclophosphamide + Corticosteroid
Severe	Yes	>5.7 mg/dl	Yes	Cyclophosphamide + Corticosteroid + Plasmapheresis
Refractory	Yes	Any	Yes	Drugs under investigation

Therapeutic

General Guidelines Vasculitis treatment is based on aggressive immunosuppression, and as a result, the complications of treatment are common and can be severe. The degree of immunosuppression should therefore depend on the severity of the disease, in order to minimize the adverse effects.

A two-phase model is used in treatment: the induction of remission phase (with more intensive immunosuppression) and the maintenance phase (less intensive therapy, aimed at decreasing the adverse effects of the immunosuppression, maintaining remission of the disease).[7,8]

Measures like vaccination, physical medicine and rehabilitation, nutritional support, oxygen therapy, treatment of comorbidities and psychosocial support all help minimize the morbidity associated with these diseases.

Induction Options (Table VIII). The limited form of the disease is defined as symptoms which affect only an organ (e.g. lung, upper respiratory airways), with systemic symptoms and without renal impairment. Therefore induction is often limited to the use of a single agent, such as corticosteroids, methotrexate or azatioprine. The early generalized form of the disease can be distinguished from the active generalized form by the absence of organ dysfunction. Both agents, methotrexate and cyclophosphamide, are currently accepted as first line therapy. The active generalized disease, where organ dysfunction is preset, should be treated with oral cyclophosphamide and corticoids.

The severe form of the disease is identified by the presence of severe renal dysfunction, DAH (diffuse alveolar hemorrhage) or some other life-threatening condition. These patients benefit from triple treatment: cyclophosphamide, corticosteroids and plasmapheresis. As additional therapy for patients with DAH, factor VII is used, as a hemostasis inducer. Disease that does not respond to cytotoxic agents and high doses of corticoids or plasmapheresis is designated refractory disease. In this case, the use of new agents is considered, such as TNF-α inhibitors (Infliximab), B cell inhibitors (Rituximab), B and T cell suppressors (MMF, mycophenolate mofetil, - Cellcept), and T Cell suppressors (Leflunomide - Arava; anti-thymocyte globulin, interferon alpha).[7,8]

Maintenance options (Table VIII) According to the general concept, during maintenance the immunosuppression is less aggressive, with minimization of the adverse effects, keeping the disease in remission. After induction of remission with cyclophosphamide, patients begin therapy with methotrexate or azathioprine.[7] Additional therapy generally consists of low doses of corticoids. The time necessary to transfer the patient from the induction to the maintenance phase has been the object of discussion: some authors suggest a 12-month course of empirical induction, others disagree, demonstrating that clinical remission can occur at the end of 3-6 months of induction therapy (see www.vasculitis.org and www.rheumatology.org).

The EUVAS (European Vasculitis Study Group) is promoting multiple studies to assess the effectiveness of different first line therapy protocols in systemic vasculitis.

Studies already completed report the following:

NORAM, comparison of methotrexate (MTX) with cyclophosphamide (CYC) in 100 patients with recently diagnosed AAV, serum creatinine lower than 150 µmol/L, and the absence of a life-threatening

TABLE VIII

Therapeutic options for induction and maintenance[4]

Induction	Ciclofosfamida Prednisolona	2mg/kg. Reduction if renal function ↓ 1 mg/kg	3-6 months (6-12 months)
Adjuvant therapy	Plasmaférese ou Metilprednisolona	7X4L 3X1g	
Maintenance	Azatioprina Prednisolona	2 mg/kg 7.5 mg	24 Months 6-24 Months

condition. Remission was achieved at 6 months in 89.8% of patients treated with MTX and in 93.5% of those treated with CYC. However, the rate of relapse after 1 year (when the medication was suspended) was very high: 69.5 % with MTX vs 45% with CYC, with an average relapse time of 13.5 months, which suggests that even in AAV without renal involvement, the medication should be withdrawn gradually.

CYCAZEREM, compared the use of azathioprine (AZA) and CYC as maintenance therapy in 155 patients with AAV and moderate renal involvement (creatinine lower than 500 µmol/L). In the first phase of the study, treatment with oral CYC (2 mg/kg/day) and prednisolone (1 mg/kg/day with gradual withdrawal of the medication to 0.2 mg/day over a 12-month period) resulted in remission in 144 patients; of these, 119 reached remission at 3 months. 7 deaths were registered during the induction and 1 patient abandoned the trial. After the induction of remission phase (3-6 months), some patients maintained CYC (1.5 mg/kg/day for 12 months, and others received AZA (2 mg/kg/day), the prednisolone dose (10 mg/day) being equal in both. In the following phase, both groups received AZA (1.5 mg/kg/day) and prednisolone (7.5 mg/day).

No differences were found between the relapse rates (15.5 AZA vs 13.7 CYC) at 18 months at the end of the study either, which suggests that withdrawal from CYC can be done after the induction of remission.

MEPEX compared plasmapheresis or the administration of pulsed methylprednisolone as standard scheme adjuvant therapy, with CYC and prednisolone in 151 patients with AAV and acute renal insufficiency. The results suggest that the renal outcome was better in the plasmapheresis group.

CHUSPAN evaluated CSS treatment and also PAN and MPA treatment with factors of poor prognosis, using pulsed CYC (0.6 g/m2/month), comparing the effectiveness of 6 or 12 pulses, in combination with corticosteroids. The trial concluded that 6 pulses of CYC were less effective in the treatment of severe PAN and MPA, particularly in relation to relapses.[29]

Other trials have been published or are currently underway, including trials to determine the therapeutic effectiveness in refractory forms of AAV using biological agents (www.vasculitis.org).

Therapeutic complications The therapy used to treat small vessel vasculitis is highly aggressive and toxic. However, the almost universal mortality of this disease, if left untreated, justifies this therapy. It is necessary to monitor bone marrow suppression and pay close attention to the existence of other infections. Severe infections, related to the treatment, occur in 10% of patients treated with cyclophosphamide[7] and are often the cause of death.

Although there is no irrefutable evidence of its effectiveness, prophylaxis with co-trimoxazole is used in patients taking high doses of cyclophosphamide.[18]

Prophylaxis of the bone demineralization, as a result of treatment with high doses of corticosteroids, consists of protection with biphosphonates and calcium supplements, without or without vitamin D. Gastric protection is also recommended.[18]

Conclusions

The designation *pulmonary renal syndrome* is used when a patient shows pulmonary involvement (alveolar vasculitis/hemorrhage) and renal involvement (rapidly progressive glomerulonephritis). Eighty percent of these cases are represented by the group of ANCA-associated vasculitis, and by Goodpasture syndrome.[30] Given that it is essential for the respective etiopathogeny, ANCA is not, however, a compulsory criteria for diagnosis, and particular emphasis should be placed on the clinical and imagiological criteria of this heterogeneous group of pathologies. Current therapy, based on immunosuppression schemes, alters the natural progression of the disease in terms of its manifestations and complications. ■

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