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Informed consent has been obtained from the patient(s).

# Pulmonary-renal syndrome : when clinical findings guide laboratory testing

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## Case description

A 57-year-old patient presented with hemoptoic sputum, dyspnea since one week, and a 6 kg weight loss over 3 months. The patient was hemodynamically stable, afebrile, tachypneic, and desaturated to 85% on room air. Laboratory tests showed leucocytes 5.8 G/l, CRP 11 mg/l, and creatinine 157 µmol/l. A chest X-ray revealed right basal condensation. Oxygen therapy was started, and he was admitted to a care unit.

### 1) Which treatment proposal is most appropriate at this stage?

- a. Anticoagulation for suspected pulmonary embolism
- b. Empirical antibiotic therapy
- c. Administration of furosemide
- d. Intravenous contrast-enhanced chest CT scan
- e. Right lateral decubitus positioning and intubation

Anticoagulation is not indicated due to a low revised Geneva score, justifying first of all additional investigations (d-dimer levels, chest CT scan). Antibiotic coverage without supplementary investigations is inappropriate in the absence of fever and an inflammatory syndrome. There were no signs of cardiac decompensation requiring diuretic treatment. Decubitus positioning with intubation should be performed in cases of massive hemoptysis [1]. The CT scan did not reveal an embolism or alveolar hemorrhage; however, showed indirect signs of pulmonary hypertension (dilation of the pulmonary trunk and right atrium), inferior retractile condensation, and diffuse thickening of the lower lobar bronchial walls.

The course of the disease was marked by the persistence of hemoptoic sputum and the rapid development of respiratory failure requiring intubation. The bronchoscopy found purulent secretions and a diffusely inflammatory mucosa in the right bronchial tree and fresh blood in the lingular bronchus area, suggesting an infectious origin. Empirical antibiotic therapy was started. Patient's condition improved, allowing for extubation and transfer to the ward. He experienced a new episode of hemoptysis, followed by a hypoxic cardiorespiratory arrest (resuscitation and intubation with return to spontaneous circulation at 10 minutes). Post-resuscitation bronchoscopy showed bloody secretions in the right middle lobe without active bleeding or endobronchial lesions. A bronchoalveolar lavage (BAL) was performed. A second scan revealed increased condensation affecting both lung fields with persistent signs of pulmonary hypertension (fig. 1).

### 2) Which statement about alveolar hemorrhage is correct?

- a. Bloody sputum systematically points to a pulmonary origin
- b. The presence of ground-glass opacities on a thoracic CT scan is indicative of alveolar hemorrhage
- c. Alveolar hemorrhages never lead to respiratory failure
- d. A strongly positive Golde score on BAL is highly suggestive of alveolar hemorrhage
- e. In cases of alveolar hemorrhage, it is not necessary to search for an underlying systemic disease

Pseudohemoptysis should be considered in the presence of hemoptoic sputum. Alveolar hemorrhage is characterized by damaged lung parenchyma, creating a shunt effect and hypoxemia. In our patient, multiple episodes of desaturation occurred due to blood-tinged mucosal plugs. Repeated

bronchoscopies revealed hemorrhagic secretions in the left lower lobe. Analysis of the BAL showed neutrophilic alveolitis (macrophages 39% [norm > 85%], lymphocytes 10% [10-15%], neutrophils 51% [<3%], eosinophils 0% [<1%]) without malignant cells. The Golde score, used for quantifying iron load in macrophages, was 120, indicating severe alveolar hemorrhage [2]. On admission, the patient presented with acute renal failure which progressively worsened. The urine sediment showed the presence of glomerular erythrocytes. The spot test revealed a sodium excretion fraction of 3.2% and a proteinuria estimated at 3.74 g/24h. Renal ultrasound ruled out an obstructive cause. The coexistence of alveolar hemorrhage and acute renal failure suggests an immunological etiology. Investigations showed slightly positive anti-nuclear antibodies (ANA) with no associated specificity, negative anti-basal membrane antibodies (anti-GBM), and the absence of anti-PR3 (<0.6 IU/mL standard <5 IU/mL) and anti-MPO (5.8 IU/mL, standard <6 IU/mL) antibodies.

**3) The clinical suspicion of ANCA vasculitis remains high. Which additional test is recommended to confirm the diagnosis?**

- a. No further examination is required
- b. Angio-MRI to look for vasculitis
- c. A new test detecting anti-PR3 and anti-MPO antibodies using Enzyme-Linked ImmunoSorbent Assay (ELISA)
- d. Contact the laboratory to request indirect immunofluorescence (IIF) if the ELISA test result is negative but suspicion of ANCA vasculitis is strong
- e. Immediate renal biopsy

ANCA can be detected primarily in two ways: through IIF on fixed neutrophils to identify perinuclear (P-ANCA) or cytoplasmic (C-ANCA) fluorescence, and through immunoassays such as ELISA to detect antibodies targeting proteinase 3 (PR3) or myeloperoxidase (MPO). IIF was the only technique available until the introduction of commercial ELISA tests in 1990. Historically, in cases of suspected ANCA vasculitis, IIF was indicated initially, followed by an ELISA test if results were positive [3-5]. A recent study showed that the sensitivity and specificity of modern immunoassays detecting anti-PR3 and anti-MPO antibodies surpass those of IIF [6]. As a result, many laboratories have changed their current practice: if ANCA vasculitis is suspected, the search for anti-PR3 and anti-MPO antibodies is preferred. IIF is reserved to confirm a positive result. However, when the ELISA test is negative, yet clinical suspicion of vasculitis remains high, IIF is still recommended [6,7]. In our case, IIF for ANCA revealed a strong P-ANCA fluorescence. Anti-MPO and anti-PR3 tests were repeated and showed a low positivity level for anti-MPO. Various confirmation tests were carried out (ImmunoDOT, ELISA, dilution tests) and confirmed the latter (fig. 2). These results were compatible with ANCA vasculitis [8]. A renal biopsy revealed a severe pauci-immune extracapillary glomerulonephritis with active and chronic lesions, thereby confirming the diagnosis (fig. 3), most likely microscopic polyangiitis (MPA) with pneumo-renal involvement.

**4) Which of the following applies to the histological diagnosis of ANCA vasculitis of the granulomatosis type with polyangiitis (GPA) or microscopic polyangiitis (MPA)?**

- a. A surgical lung biopsy has a favorable risk-benefit profile
- b. The best diagnostic yield is obtained from skin biopsies
- c. Transbronchial biopsies are very sensitive
- d. In cases of renal involvement, a (renal) biopsy is indicated to establish the diagnosis
- e. The presence of secondary focal-segmental glomerulonephritis is characteristic of MPA

If ANCA vasculitis is suspected, histological findings are necessary to support the diagnosis. Biopsies can be carried out on various tissues affected by the disease, such as the skin, kidney, lung, or nervous tissue. A surgical lung biopsy can be useful in identifying typical histopathological features. Transbronchial biopsy, although less invasive, is less sensitive. A negative histological finding does not rule out the possibility of GPA or MPA [9]. Skin biopsies may be lacking in specificity. In fact, leukocytoclastic vasculitis and their histological entity can be found in other diseases. Renal biopsies are particularly useful in identifying signs of active vasculitis [10]. In cases of MPA or GPA with rapidly progressive renal damage, the lesions observed on biopsies consist of pauci-immune extracapillary glomerulonephritis [11-13]. Almost all patients with severe pauci-immune glomerulonephritis present with positive ANCA [14]. In our patient's case, the differential diagnosis includes GPA, MPA, and eosinophilic granulomatosis with polyangiitis (EGPA). EGPA is unlikely in the absence of peripheral eosinophilia and asthma. The diagnosis of MPA is accepted based on the presence of P-ANCA and anti-MPO antibodies, along with the absence of ENT involvement (with typical characteristics of GPA), thereby justifying the initiation of immunosuppressive treatment.

**5) Which of the following statements regarding the treatment of ANCA vasculitis is correct?**

- a. Organ damage severity and the presence of a life-threatening disease do not determine the choice of immunosuppressive treatment
- b. High-dose corticosteroid therapy is considered an adequate induction regimen for patients with severe organ failure
- c. Once the induction phase is over, the risk of infection becomes identical to that of the general population
- d. A complement C5a receptor antagonist (avacopan) may be used instead of rituximab or cyclophosphamide for the induction phase in ANCA vasculitis
- e. During the induction phase, rituximab may have a more favorable adverse event profile compared to cyclophosphamide

An induction regimen combining glucocorticoids with cyclophosphamide or rituximab is indicated in the presence of organ damage or a life-threatening disease (active glomerulonephritis, alveolar hemorrhage) [15]. A recent study demonstrated the non-inferiority of reduced glucocorticoid dosage to decrease infectious complications [16]. The ADVOCATE study proposes avacopan, a complement C5a receptor antagonist, as an alternative to glucocorticoids in conjunction with standard therapies such as rituximab or cyclophosphamide. Compared to glucocorticoids, this drug presents an advantageous risk-benefit profile and non-inferiority in achieving remission at 26 weeks and even superiority at 52 weeks [17]. The non-inferiority of rituximab compared to cyclophosphamide has also been shown, along with a more favorable risk profile [18-20]. In our patient, a treatment combining prednisone and rituximab was started, and there was no indication for plasma exchange (peak creatinine level 267  $\mu\text{mol/l}$ , endpoint 142  $\mu\text{mol/l}$ ). The outcome was favorable with no recurrence of hemoptysis and stabilization of renal function.

In conclusion, this patient was not screened for ANCA due to very low anti-MPO positivity. IIF was carried out at a later stage, upon multidisciplinary advice [21], followed by a renal biopsy confirming the diagnosis. IIF and ELISA are two complementary diagnostic tools that should be interpreted within the clinical context. ANCA vasculitis is characterized by its heterogeneous clinical presentation. Confirmation by tissue biopsy is generally warranted. Compared with other organs, kidney biopsy is preferred due to its high diagnostic yield and the ability to quantify the severity of the lesion. However, there is a risk of significant complications, therefore a personalized assessment of the risk-benefit ratio is essential. Severe organ damage or life-threatening conditions determine the type of treatment.

Infectious complications related to the disease itself or to the induction therapy remain the main cause of mortality in the first year [22]. The risk of recurrence of the disease is approximately 30%, highlighting the need for close immunological profile follow-up [23].

### **Answers**

1.d 2.d 3.d 4.d 5.e

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## **Statements**

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### **Informed consent statement**

Written informed consent is available for publication

### **Conflict of interest statement**

The authors have declared that they have no potential conflicts of interest.

### **Author contribution**

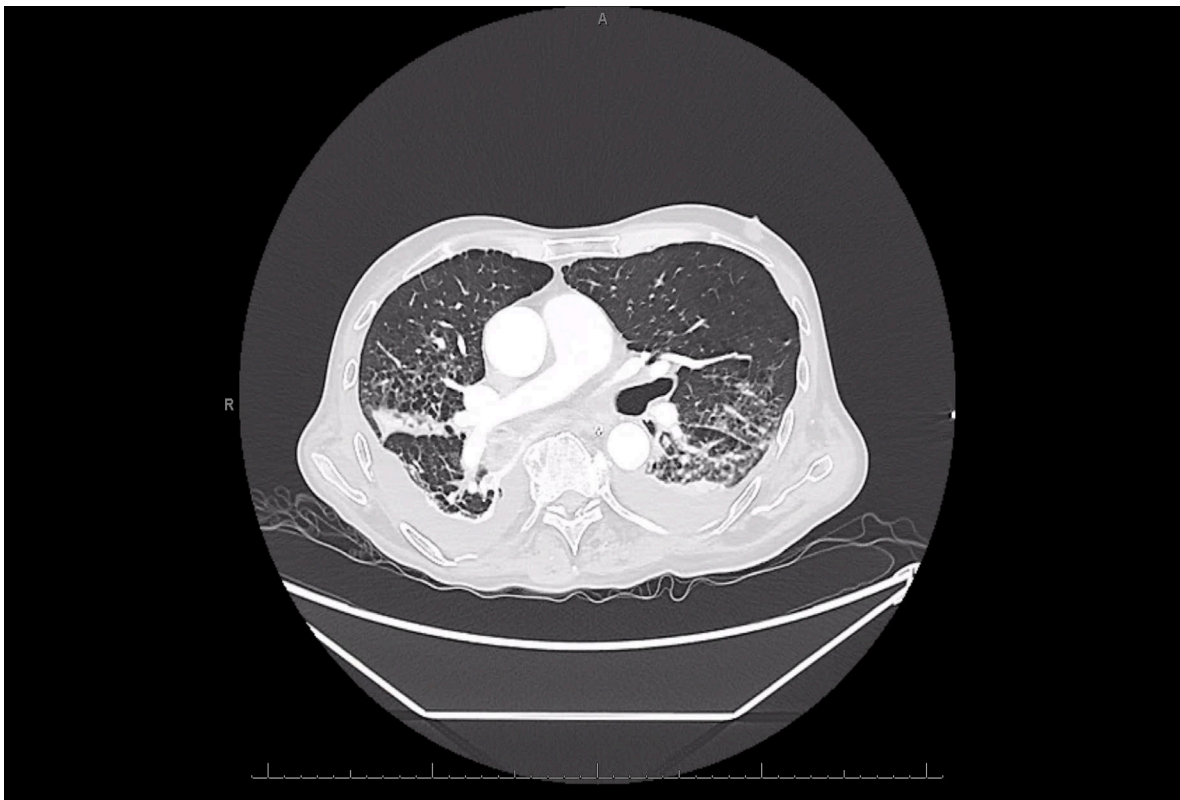
Concept, Aristidis Peidis and Romain Bühler ; Writing, revision, editing, Romain Bühler, Aristidis Peidis, Lionel Arlettaz, Thierry Bonjour ; Supervision, Thierry Bonjour. All authors have read the submitted manuscript and are jointly responsible for all aspects of the work.

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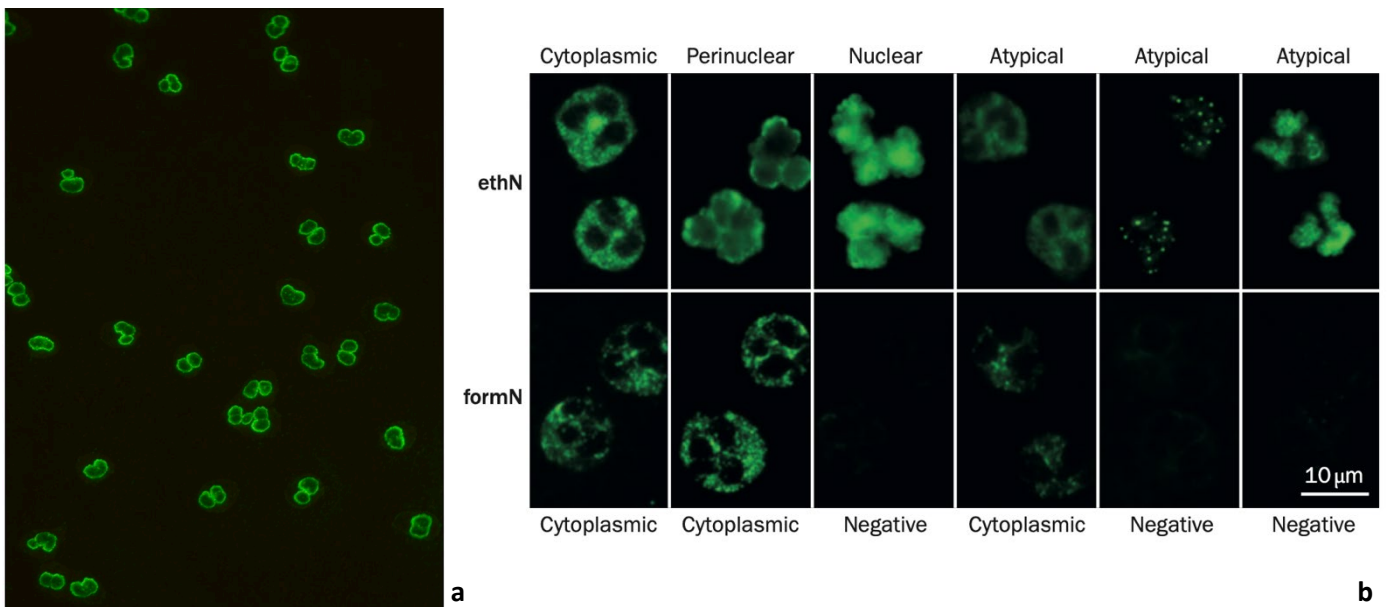
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## Figures and Table

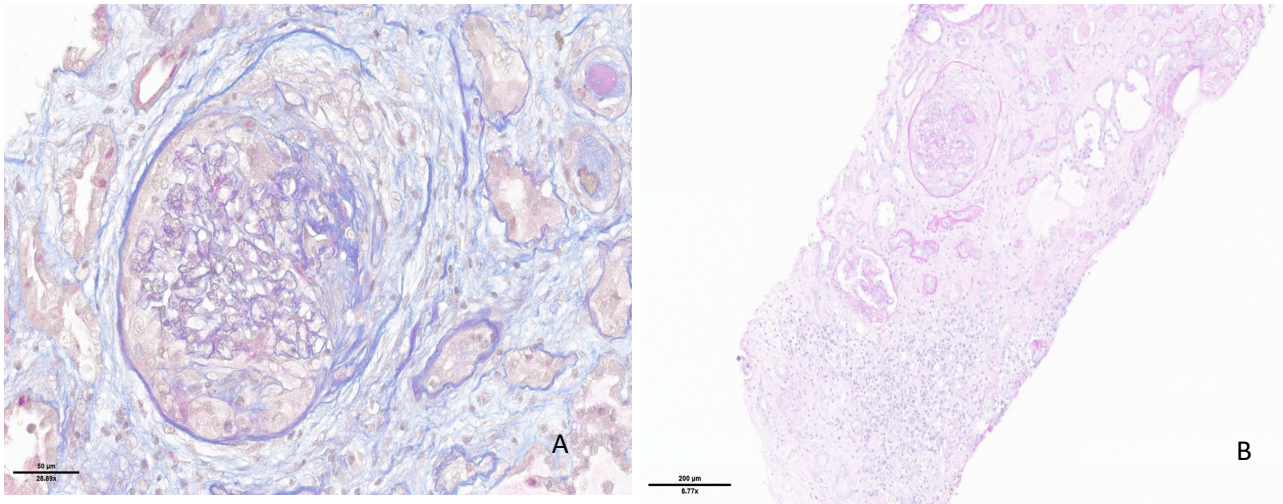


**Figure 1.** Chest CT scan: increase in size and number of condensations affecting both lung fields, presence of centro-lobular emphysema, bilateral pleural effusions up to 3 cm on each side. Dilatation of the pulmonary artery trunk (from the final thoracic CT report of 13.09.2022).



**Figure 2a.** Immunofluorescence on ethanol-fixed neutrophils, with perinuclear fluorescence (P- ANCA), INOVA slide (patient serum).

**Figure 2b.** IIF image of serum samples showing C-ANCA, P-ANCA and A-ANCA patterns on ethanol and formalin-fixed human neutrophils (from : Csernok E, Moosig F. Current and emerging techniques for ANCA detection in vasculitis. Nat Rev Rheumatol. 2014 Aug;10(8):494-501, reprinted with permission).



**Figure 3. Selected extracts from histopathological sections.** Left native kidney biopsy showing 3 glomeruli (1 in panel A, 2 in panel B), surrounded by fibrous crescents. The non-sclerosed glomeruli have an active extracapillary proliferative component. There are no endocapillary proliferation components and no visible mesangial or membrane deposits. At the tubular and interstitial levels, there is a minimal mononuclear inflammatory component without granuloma.

**A)** Glomerular crescent, PAS staining, magnification approx. 200 x

**B)** Mononuclear infiltration with no visible granulation. Haematoxylin-eosin staining, at a much lower magnification

**C)** Final pathologist's report (Dr S. Rotman, CHUV) on the biopsy of the native kidney : pauci- immune extracapillary glomerulonephritis with :

- active lesions :

- extracapillary proliferation component with :

- 6 crescent cells with necrosis in 22 glomeruli

- 2 fibrocellular crescents on 22 glomeruli

- minimal mononuclear interstitial inflammation (<5%)

- no image of vasculitis

- chronic lesions :

- glomerular sclerosis (8/22: 32%)

- extracapillary proliferation component with :

- 10 fibrous crescents on 22 glomeruli

- interstitial fibrosis (80%)

- moderate arteriosclerosis

- mild arteriolar hyalinosis

**Commentary :**

Based on the results of the immunological work-up, this pauci-immune extracapillary glomerulonephritis is consistent with ANCA vasculitis

<b>DESCRIPTIONS</b>			
	<b>Microscopic polyangiitis (MPA)</b>	<b>Granulomatosis with polyangiitis (GPA)</b>	<b>Eosinophilic granulomatosis with polyangiitis (EGPA)</b>
<b>Definition</b>	Necrotic vasculitis with few or no immune deposits, predominantly affecting small vessels (capillaries, venules, arterioles and small arteries). Necrotic arteritis involving small to medium-sized arteries may be present. Glomerulonephritis is very common. Pulmonary capillaritis often occurs. Granulomatous inflammation is absent.	Necrotic granulomatous inflammation most often involving the upper and lower respiratory tract and necrotic vasculitis predominantly affecting small to medium-sized vessels (capillaries, venules, arterioles, arteries and veins). Necrotic glomerulonephritis is common.	Necrotic, eosinophil-rich granulomatous inflammation often involving the respiratory tract and necrotic vasculitis predominantly affecting small to medium-sized vessels and associated with asthma and eosinophilia.
<b>Clinical characteristics</b>	Long prodromal phase with B symptoms, followed by rapidly progressive glomerulonephritis; frequent involvement of the airways and lungs (10-30%), with diffuse alveolar hemorrhage being the most frequent manifestation.  Symptomatology relatively similar to GPA.	Clinical triad : - upper airways (sinusitis, otitis, nasal septum ulcerations, nasal polyps, gingival hyperplasia, bronchial or subglottic stenosis) - lungs (chest pain, dyspnea, hemoptysis, pulmonary nodules, infiltrations, cavitations) - kidneys (not necessarily present in the initial clinical presentation but may evolve into rapidly progressive glomerulonephritis and impaired renal function)  Approximately 60% of patients present with ENT involvement at the start of a GPA.	Peripheral blood hypereosinophilia; peripheral neuropathy (multiple mononeuritis); asthma (almost a universal manifestation preceding the clinical course of vasculitis); upper airways are frequently affected (obstruction, serous otitis, sinusitis, nasal polyposis); myocardial involvement (poor prognostic factor).  Glomerulonephritis and alveolar hemorrhage are rare.

<b>Laboratory</b>	Anti-MPO (p-ANCA) 50-75% of cases	Anti-PR3 (c-ANCA) > 90% of cases	Anti-MPO (p-ANCA) 45-70% of cases Eosinophilia			
<b>Histopathology</b>	Focal necrotic vasculitis of small vessels without granuloma; pauci-immune necrotic glomerulonephritis.	Small to medium-sized necrotic vasculitis of the vessels; granulomatous inflammation of the airways; pauci-immune necrotic glomerulonephritis.	Necrotic vasculitis of small to medium-sized vessels with eosinophilic infiltrates and necrotic granulomas.			
<b>TREATMENTS</b>						
	<b>Active MPA/GPA</b>		<b>Active EGPA</b>			
	Early-onset systemic disease*	Generalized disease*	Severe illness*	Early-onset systemic disease*	Generalized disease*	Severe illness*
<b>Induction phase</b>	glucocorticoids or avacopan + methotrexate or mycophenolate mofetil	high-dose glucocorticoids or avacopan + cyclophosphamide or rituximab	plasmapheresis according to criteria**	glucocorticoids	glucocorticoids + cyclophosphamide or rituximab	
<b>Maintenance phase</b>	glucocorticoid withdrawal or stop avacopan + switch to rituximab or azathioprine or methotrexate			glucocorticoid withdrawal + switch to azathioprine or methotrexate or mepolizumab or rituximab		
	<i>After 24-48 months :</i> stop glucocorticoids or avacopan stop rituximab or azathioprine or methotrexate			<i>After individualized duration :</i> stop glucocorticoids stop azathioprine or methotrexate or mepolizumab or rituximab		

\*Early systemic disease = systemic symptoms other than upper or lower airway involvement, with no change in renal function or the function of other vital organs.

\*Generalized disease = clinically similar to early systemic disease but with impaired kidney function

\*Severe disease = characterized by damage to vital organs and life-threatening conditions (glomerulonephritis, alveolar hemorrhage, retro-orbital damage, meningeal damage, cardiac damage, mesenteric involvement, complex mononeuritis).

**\*\*Severe GPA or MPA and active glomerulonephritis (creatinine > 300 µmol/l) despite treatment with cyclophosphamide and glucocorticoids.**

**Table 1.** Classification and treatment of ANCA vasculitis (adapted from: classification according to the international Chapel Hill Consensus Conference (CHCC 2012) and Duarte AC, Ribeiro R, Macedo AM, Santos MJ. ANCA-associated vasculitis: overview and practical issues of diagnosis and therapy from a European perspective. Porto Biomed J. 2023 Dec 13;8(6) :e237.)