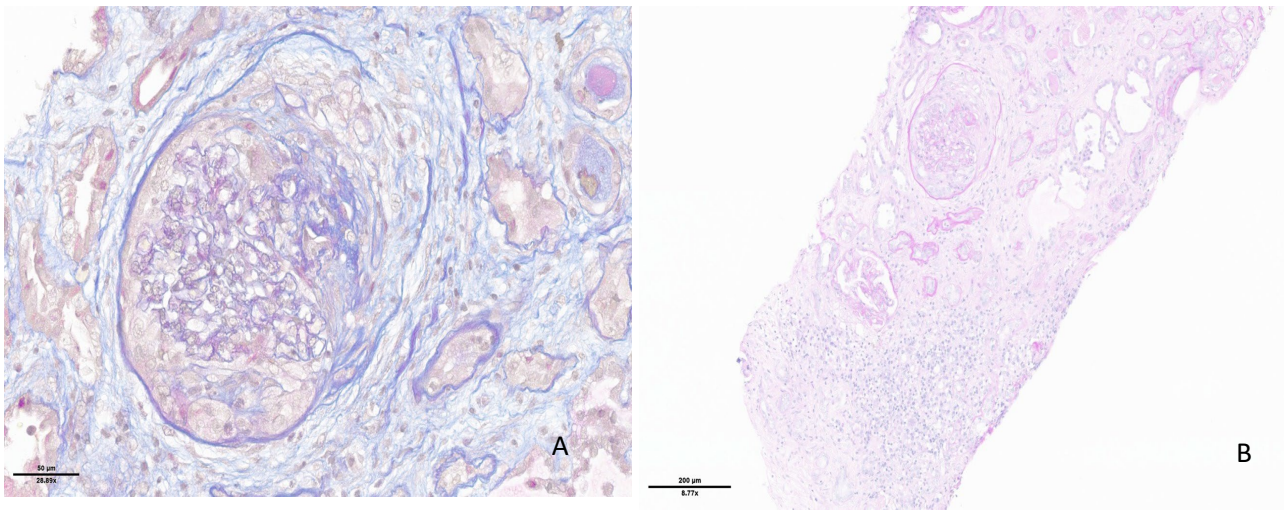

Figure 3. Selected extracts from histopathological sections. Left native kidney biopsy showing 3 glomeruli (1 in panel A, 2 in panel B), surrounded by fibrous crescents. The non-sclerosed glomeruli have an active extracapillary proliferative component. There are no endocapillary proliferation components 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

DESCRIPTIONS			
	Microscopic polyangiitis (MPA)	**Granulomatosis with polyangiitis (GPA)**	**Eosinophilic granulomatosis with polyangiitis (EGPA)**
Definition	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.
Clinical characteristics	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.

<table>
<tr><td>Laboratory</td><td colspan="2">Anti-MPO (p-ANCA)
50-75% of cases</td><td>Anti-PR3 (c-ANCA)
> 90% of cases</td><td colspan="3">Anti-MPO (p-ANCA)
45-70% of cases
Eosinophilia</td></tr>
<tr><td>Histopathology</td><td colspan="2">Focal necrotic vasculitis of small vessels without granuloma; pauci-immune necrotic glomerulonephritis.</td><td>Small to medium-sized necrotic vasculitis of the vessels; granulomatous inflammation of the airways; pauci-immune necrotic glomerulonephritis.</td><td colspan="3">Necrotic vasculitis of small to medium-sized vessels with eosinophilic infiltrates and necrotic granulomas.</td></tr>
<tr><td colspan="7"><u>TREATMENTS</u></td></tr>
<tr><td></td><td colspan="3">Active MPA/GPA</td><td colspan="3">Active EGPA</td></tr>
<tr><td></td><td>Early-onset systemic disease*</td><td>Generalized disease*</td><td>Severe illness*</td><td>Early-onset systemic disease*</td><td>Generalized disease*</td><td>Severe illness*</td></tr>
<tr><td rowspan="2">Induction phase</td><td rowspan="2">glucocorticoids or avacopan
+
methotrexate or mycophenolate mofetil</td><td colspan="2">high-dose glucocorticoids or avacopan
+
cyclophosphamide or rituximab</td><td>glucocorticoids</td><td colspan="2">glucocorticoids
+
cyclophosphamide or rituximab</td></tr>
<tr><td></td><td>plasmapheresis according to criteria**</td><td></td><td colspan="2"></td></tr>
<tr><td rowspan="2">Maintenance phase</td><td colspan="3">glucocorticoid withdrawal or stop avacopan
+
switch to rituximab or azathioprine or methotrexate</td><td colspan="3">glucocorticoid withdrawal
+
switch to azathioprine or methotrexate or mepolizumab or rituximab</td></tr>
<tr><td colspan="3"><u>After 24-48 months :</u>
stop glucocorticoids or avacopan
stop rituximab or azathioprine or methotrexate</td><td colspan="3"><u>After individualized duration :</u>
stop glucocorticoids
stop azathioprine or methotrexate or mepolizumab or rituximab</td></tr>
</table>

*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.)