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ANCA-associated glomerulonephritis : insights into etiology, pathogenesis, and prognosis

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A good surgeon may be wrong, but he is never in doubt.
Old surgeon's saying

A good scientist may be right, but he is always in doubt.
R.A.F. de Lind van Wijngaarden



Chapter 8

Summary

The term vasculitis refers to vascular inflammation. In patients with systemic vasculitis, vascular inflammation can occur throughout the body, causing organ damage and eventually failure of the organ in which the diseased vessel is located. This can cause complaints which may be either general, such as malaise and fever, or organ-specific, such as localized joint pain, nose bleeds, and hemoptoe. Within the spectrum of vasculitis, the different diagnoses are classified on the basis of organ involvement, and laboratory findings, with anti-neutrophil cytoplasm autoantibodies (ANCA) being a classifying hallmark of the group of ANCA-associated vasculitides. This thesis considers three diagnoses within this spectrum: Wegener's granulomatosis, microscopic polyangiitis, and renal-limited vasculitis.

The discussion about whether these diagnoses are separate diseases within one spectrum or different forms of a single disease is still unfinished. Next to many similarities, there are distinct differences. For example, in Wegener's granulomatosis, typically organized inflammatory lesions (granulomas) are observed. Moreover, upper airway involvement is common. Microscopic polyangiitis can be distinguished from Wegener's granulomatosis by the absence of granulomas and upper airway involvement. However, in daily clinical practice the distinction is often not obvious and sometimes difficult to make. Renal-limited vasculitis is characterized by the absence of extra-renal organ involvement.

Renal injury in ANCA-associated vasculitis can lead to inflammation and scarring of components of the renal filtering system: the glomeruli, the tubuli, and the interstitium. Upon disease progression, treatment options include temporary or permanent dialysis or renal transplantation.

Untreated ANCA-associated vasculitis usually leads to early death. Although no cure has been found yet, there are several therapeutic options. Next to renal replacement therapies, such as dialysis or transplantation, treatment options include anti-inflammatory therapies, a few of which are discussed in this thesis.

When a patient is diagnosed with vasculitis, obvious questions that rise are: "What are the treatment options?", "What is my prognosis?", and "How did I get this disease?". A major challenge in vasculitis research is to find suitable answers to these questions. This thesis contributes to finding these answers. In the various chapters short and long term prognoses of distinct patient groups who have followed distinct therapeutic regimens are analyzed. Furthermore, we explored which factors contribute to these prognoses. In **chapter 2**, those patients that already had severe renal failure at diagnosis (serum creatinine >



500 $\mu\text{mol/L}$) were subject of investigation. Their one year outcome was analyzed. In **chapter 3**, the group with renal injury, so severe that they required dialysis was investigated. Long term outcome (after five years) is described in **chapter 4**. In this study patients within the spectrum from mild to severe renal failure at diagnosis were analyzed. In these patients the influence of ear, nose, and throat (ENT) involvement on the progression of renal disease was analyzed, which is described in **chapter 5**. Finally, **chapter 6** is dedicated to the description of the most plausible hypotheses on the etiology of vasculitis.

To find an answer to the question on prognosis for a newly diagnosed patient with severe renal involvement (serum creatinine $> 500 \mu\text{mol/L}$), it was investigated which factors predict a good outcome after one year (**chapter 2**). It appeared that the percentage of normal glomeruli in the diagnostic renal biopsy was positively correlated to dialysis independency at one year. It also became clear that plasma exchange as adjunct to standard therapy - as opposed to intravenous methylprednisolone- protected the patient from dialysis dependency at one year. For those patients who were not on dialysis, a better renal function at one year was predicted by: better renal function at diagnosis, younger age, and a higher percentage of normal glomeruli and less tubular atrophy in the diagnostic biopsy. From these observations, it can be concluded that the part of the kidney which does not participate in the disease process has major influence on one-year prognosis.

In **chapter 3**, a study is described which targets the group of patients with the worst state of disease: those who were dialysis dependent at diagnosis. Within this group there is a 25% death rate after the first year. A large part of this group dies of therapy-related causes, mainly due to immunosuppression followed by infection and sepsis. In this study, it was investigated whether the hazards of strong immunosuppressive therapy exceeded its benefits, and whether it was justified to accept that in case of a small chance on therapeutic success, the patient continues dialysis treatment without any hope on renal function recovery. From this investigation, it could be concluded that even if the patient's renal biopsy shows a very bad histological picture, the chance of being dialysis independent always exceeds the chance of dying at one year after diagnosis, as long as the patient receives plasma exchanges as adjunct to standard therapy. Another observation in this study was that therapy-related death only occurred between 3 and 12 months after diagnosis, while renal recovery usually took place within the first 3 months. This finding underlines that safer treatment strategies are necessary for patients with ANCA-associated vasculitis who are dialysis dependent at diagnosis.



The study described in **chapter 4** addresses the question which factors at time of diagnosis predict outcome at 5 years. The patients included in the analysis had a broad spectrum of renal involvement: from mild to severe. Some were even dialysis dependent. Clinical factors that are predictive of better renal and patient outcome were younger age, better renal function at diagnosis, and the absence of ANCA directed against myeloperoxidase (MPO-ANCA). Moreover, findings in the diagnostic renal biopsy were predictive of renal outcome. These encompass the percentage of normal glomeruli, the percentage of fibrous crescents, and tubular necrosis. This is a remarkable result, since it illustrates that even prognosis at long term is determined by findings in the diagnostic renal biopsy.

Ear, nose and throat (ENT) involvement is common in Wegener's granulomatosis. In diagnostic renal biopsies, less acute and chronic damage has been observed in Wegener's granulomatosis, as compared to microscopic polyangiitis. The most recent hypothesis to explain this observation is that patients with Wegener's granulomatosis are diagnosed earlier, since ENT involvement facilitates clinical diagnosis in an earlier stage. The first study that addresses the differences in renal histology in patients with and without ENT involvement is described in **chapter 5**. It appeared that patients with ANCA-associated glomerulonephritis and ENT involvement have more normal glomeruli, less chronic glomerular and tubular lesions on histology, and a better renal function. This could be explained by earlier diagnosis, but also by a difference in pathogenesis.

The question how ANCA production is initiated in patients is addressed in **chapter 6**. The chapter discusses the different hypotheses on which factor is responsible for the initiation of ANCA production. Until this day, no factor can be held solely responsible for the presence of ANCA in patients. The most plausible hypothesis is that an interplay of different environmental factors, such as silica, bacterial and viral infection, and drugs, upon genetic susceptibility creates the condition that ANCA production can be initiated.

In conclusion, this thesis discusses different factors that may play a role in ANCA production in patients with ANCA-associated vasculitis. Moreover, it addresses which factors within different groups of patients are predictive of short and long term outcome. One study described in this thesis reveals that even if the renal biopsy shows an abundance of histological lesions, the chance of recovery exceeds the chance of dying of therapy-related causes, if the patient is treated with plasma exchange as adjunct to standard therapy. Other studies



Summary

show that certain lesions predict not only one-year, but also five-year outcome, and that the status of the patient at five years is to a large extent determined by the status of the patient at one year. This implies that therapy should be targeted at safely improving renal function as quickly as possible. Another analysis described in this thesis reveals that ENT involvement as a result of vasculitis is relatively beneficial, since renal damage and renal function deterioration are less advanced. In spite of all efforts, questions like "What are the treatment options?", "What is my prognosis?", and "How did I get this disease?" still remain unanswered. Nonetheless, this thesis does render insight into the different prognoses of distinct patient groups and the way prognosis is determined by the clinical picture and the renal biopsy of the individual patient.