THE FIVE TYPES OF GLOMERULONEPHRITIS CLASSIFIED BY PATHOGENESIS, ACTIVITY, AND CHRONICITY (GN-AC)

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ABSTRACT

Glomerulonephritis (GN) is a diverse group of immune-mediated disorders. Currently, GN is classified largely by histological patterns that are difficult to understand and teach and most importantly, do not indicate treatment choices. Indeed, altered systemic immunity is the primary pathogenic process and the key therapeutic target in GN. Here, we apply a conceptual framework of immune-mediated disorders to GN guided by immunopathogenesis and hence immunophenotyping: 1) Infection-related GN require pathogen identification and control, 2) Autoimmunity-related GN, defined by presence of autoantibodies, and 3) Alloimmunity-related GN in transplant recipients both require the suppression of adaptive immunity in lymphoid organs and bone marrow, 4) Autoinflammation-related GN, e.g., inborn errors of immunity diagnosed by genetic testing, requires suppression of single cytokine or complement pathways, and 5) Monoclonal gammopathy-related GN requires B or plasma cell clone-directed therapy. A new GN classification should include a) disease category, b) immunological activity to tailor the use of the increasing number of immunomodulatory drugs, and c) chronicity to trigger standard CKD care including the evolving spectrum of cardio-renoprotective drugs. Certain biomarkers allow diagnosis and the assessment of immunological activity and disease chronicity without kidney biopsy. These five GN categories and a therapy-focused GN classification is likely to overcome some of the existing hurdles in GN research, management, and teaching by reflecting disease pathogenesis and guiding the therapeutic approach.

As glomeruli function as high flow filters that produce a substantial ultrafiltrate, they are vulnerable to inflammatory injury from a variety of causes, resulting in a diverse range of causes of GN. Understanding, treating, studying, and teaching glomerulonephritis (GN) is difficult, not only due to the diversity of diseases themselves, but also because there is no simple logical classification to underpin the long list of disease entities that comprise the GNs.

Currently, GN is categorized based largely on histopathological lesion patterns, with primary and secondary forms and a myriad of differential diagnoses for each entity. There are historical reasons why we group GN in this manner, specifically the development of kidney biopsy and the capacity of light microscopy to describe patterns of glomerular injury, based largely on changes in cell number, deposits and matrix proteins in different parts of the glomerulus. The introduction of immunohistochemistry for immunoglobulins and complement, and electron microscopy extended this paradigm. However, the evolution of immunophenotyping and the advent of genetics demonstrated that the same histological lesions can develop from different disorders that require completely different treatments. Terms such as membranoproliferative GN (MPGN), focal segmental glomerulosclerosis (FSGS), and complement factor 3 GN (C3GN) are examples of the focus on lesional patterns that remain in use in describing and defining glomerular diseases, despite their diverse origins and need for different treatments. Classifying diseases caused by different processes primarily according to pathology was useful when using generic therapies such as glucocorticoids, which although effective in some conditions, in other diseases either need to be combined with additional immunomodulatory therapies or are not indicated. In addition, nomenclature and classification systems tend to drive kidney-focused research, e.g., using each emerging -omic technology to repeatedly characterize kidney injury, inflammation, fibrosis, and atrophy at an increasingly granular level within the kidney itself, while answers to the origin and persistence of immune-mediated GN can only be found outside the kidney.

Kidney biopsy confirms the GN diagnosis, helps to define immunological activity, and informs the degree of irreversible damage. However, a kidney-focused approach has impeded conceptual advances regarding disease categories. In addition, this approach has had limited impact on understanding how to control the aberrant immune mechanisms that induce and maintain GN by producing nephritogenic humoral and cellular immune effectors from outside the kidney.

To overcome some of these hurdles, we propose first to acknowledge that as GN are primarily immune-mediated disorders and to categorize GN accordingly. In addition, we propose to classify them by immunological activity (A) and chronicity (C) in a simple “GN-AC” matrix (Table 1). We discuss how approaching GN from an immunological perspective and positioning immunophenotyping at the center of the diagnostic approach has multiple important implications for GN management, treatment, education, and research.

GN-AC MATRIX STEP 1: THE TYPE OF GN

Defining GN by general categories of immune-mediated disorders.

Immune-mediated disorders can be dissected into five categories defined by the key underlying immune-mechanisms, i.e., infection, autoimmunity, alloimmunity, autoinflammation or monoclonal gammopathy.

Infection-related GNs arise from host defense against an acute, subacute of persistent infection somewhere in the body with three main immunologic mechanisms. 1. Post-

streptococcal GN arises for the capacity of group A β-haemolytic streptococci antigens to activate complement directly or by inducing production of anti-factor B antibodies, mimicking a transient complementopathy. 2. Other infection-related GN are caused by deposition of circulating immune complexes in the glomerulus related to : (i) primary or secondary (acquired or iatrogenic) immunodeficiencies that predispose to the severity or persistence of infection; (ii) colonization of implanted device such as catheters; (iii) host defense-escape mechanisms proper of certain pathogens, such as Schistosoma. Host defense against pathogens involves innate and adaptive immunity and can mimic an autoimmune disease, including transient positivity to anti-nuclear antibodies, cryoglobulines and other autoimmunity markers. 3. Cytotoxic effects of pathogens that can infect podocytes such as HIV, EBV, arbovirus, parvovirus B19 or SARS-CoV-2 causing a podocytopathy, particularly in carriers of high-risk APOL1 genotype. In rare cases, persistent infections can also cause AA amyloidosis.

Therapeutic approach. Even if the immune response contributes locally to glomerular injury, the primary therapeutic target in infection-related GNs is the infection itself. Infection-related GN may spontaneously resume once host defense is able to eliminate the pathogen 10, while it persists when pathogen keeps releasing antigens that maintain the respective immune response. Without controlling the infection, the use of immunosuppressants is questionable and may even be counterproductive via their capacity to impair host defense against the infectious agent. For example, a diagnosis of endocarditis-related GN mandates the cure of endocarditis and not the use of glucocorticoids to control glomerular inflammation. Improvements in socioeconomic conditions at a population level has reduced the incidence and impact of these diseases.

Autoimmunity-related GNs arise from adaptive immunity against a single or several of a wide spectrum of self-antigens. Even if the clinical presentations and histological lesions patterns differ depending on the localization of the self-antigens, the mechanisms of the underlying adaptive immune response share some common features. Autoimmunity arises from a loss of tolerance to which genetic and environmental factors contribute. Once tolerance is lost, cellular and humoral autoimmunity develops so that multiple adaptive and innate components may mediate injury. Sometimes autoimmunity is transient, explaining spontaneous remissions of some cases of anti-PLA2R autoimmune GN. Once long-term immune memory has formed, it manifests as clones of autoreactive memory T and B cells in the lymphoid organs and as long-lived plasma cells in their bone marrow niches that is similar to immune memory after infection or vaccination. Tissue-resident T memory cells have been described in many autoimmune diseases including the kidney and intrarenal tertiary lymphoid organs with T and B cells may be present. Re-exposure or persistent exposure to antigen in an immunologically “dangerous” context triggers antigen-specific immunological activity, which either presents as persistent or relapsing disease activity, depending on many levels of regulation. Autoimmunity is always oligo- or polyclonal but can center on one or only a few antigenic epitopes. Measurement of serum autoantibodies to some nephritogenic autoantigens predict immunological disease activity well, e.g., in anti-GBM disease or in anti-PLA2R autoimmune GN. However, in other conditions, while autoantibodies are relevant to disease, serum titers do not predict activity well enough to predict outcome or meaningfully guide therapy. This may at least in part be due to the multiple autoantigens involved in lupus

nephritis, the multiple B cells epitopes detected in anti-MPO antibody assays in people with MPO-ANCA-associated GN, or antibodies targeting different forms of IgA in IgA nephropathy Therapeutic approach. Treatments that restore tolerance by selectively eliminating the causative autoreactive lymphocyte clones or by selectively modulating their activity are not yet available. Therefore, we remain with therapies targeting the various elements of adaptive immunity that are common to many autoimmune GNs. Drugs used in this context include azathioprine, mycophenolate mofetil, calcineurin inhibitors, B cell-depleting agents, and belimumab. More recently, plasma cells have become a therapeutic target, with trials using proteasome inhibitors or anti-CD38 IgG. In addition, glucocorticoids are effective in this regard and suppress inflammation in the kidney. This dual effect of glucocorticoids is not shared by the newer immune modulators, which may explain why steroids are still in use despite their significant metabolic toxicities. Complement C5aR inhibition can at least partially replace glucocorticoids in active ANCA-associated vasculitis (with rituximab) and may have a role in other highly active autoimmune GNs. An ultimate cure for autoimmune-GNs would selectively eliminate or silence all T and B cell clones responding to the antigenic epitope. Therefore, a “clone-directed therapy”, is a conceptually promising approach also for autoimmune GNs, as is the use of tolerogenic platforms that aim to selectively modulate the activity of these clones Alloimmunity-related GNs develop in patients that received an allograft of a solid organ, bone marrow or cells . The adaptive immune response is in some ways conceptually like that of autoimmunity, although in classical alloimmunity there is no response against the self, and there is also more evidence in alloimmunity for a key role for CD8+ T cells via donor-specific alloantigenic peptides being presented in the context of MHC class I molecules. While alloreactive CD8+ T effector cells are important, donor-specific antibodies are also crucial, especially in glomerular lesions. Immunity is directed against numerous HLA and non-HLA antigens. As the spectrum of donor antigens is wide, alloimmunity is polyclonal and biomarkers that would allow a precise monitoring of the activity of alloimmunity are difficult to define. Therapeutic approach. Allo- and autoimmunity involve similar elements of the adaptive immune system, therefore, similar drugs are currently used to control alloimmunity in general and alloimmunity-related GNs. The precise alloantigens or their epitopes triggering GN are difficult to define, a hurdle for the development of any antigen-specific therapy. Whether complement inhibitors could improve the outcome of alloimmunity-related GNs is currently unknown. Autoinflammation-related GNs develop from inborn errors of immunity and therefore require genetic testing to establish the diagnosis (Figure 1). For example, genetic variants leading to overactivation of IL-1, TNF or type I interferon signaling pathways can be sufficient to cause systemic and tissue inflammation causing organ damage. Genetic complementopathies leading to C3GN belong to this category and environmental co-factors may impose a second hit to trigger kidney injury. Combinations with autoimmune forms of C3GN occur. Therapeutic approach. Inborn errors of innate immunity leading to GN do not require the use of unspecific immunosuppressants because the adaptive immune system is not involved and there is often a single dysregulated pathway mediating disease. Innate glomerular inflammation should be controllable by selective blockade of the affected cytokine pathway, e.g., anti-IL-1, anti-TNF, or anti-type I interferon, respectively 34. Inborn errors of the alternative complement pathway belong to this category and such forms of e.g., C3GN should be treatable with a specific complement

inhibitor, unless a mutated protein favors secondary autoimmunity 33. Such a C3GN would be categorized with and managed within the autoimmune GN framework and benefit from immunosuppressants to suppress adaptive immunity. Monoclonal gammopathy-related GNs arise from a single B cell or plasma cell clone that produces a nephrotoxic immunoglobulin or immunoglobulin component. Such monoclonal gammopathies of renal significance (MGRS) exemplify the management principle that targeting the primary problem, in this case the pathogenic clone in the bone marrow, is essential. Targeting the kidney with anti-inflammatory or anti-fibrotic drugs is of little use without targeting the disease-inducing clone in the bone marrow. In an analogous manner, auto- and alloimmunity-related GNs involve autoreactive clones that as well as infiltrating the kidney, themselves, produce nephritogenic antibodies in secondary lymphoid organs and bone marrow, arguing against a solely kidney-focused approach to immunotherapy of the GNs.

Therapeutic approach. ”Clone-directed therapy” with drugs targeting B cells or plasma cells producing the nephrotoxic immunoglobulin or immunoglobulin component following the treatment algorithms for multiple myeloma is the standard approach for MGRS including GN.

Summary: The last decade has witnessed unprecedented progress in the treatment of GNs because of an increasing understanding of the causative mechanism and the interacting innate and adaptive immune system. The latter implies a full pipeline of novel (and costly) immunomodulatory drugs that warrant careful use where effective and no use where not. The GN-AC classification system overcomes some of these hurdles. Where non-invasive biomarkers of the GN-AC criteria become available, kidney biopsy may become dispensable, e.g., in autoimmune GN of the PLA2R type or in multiple myeloma-related GN. Research on the immunopathogenesis of the GN may benefit from a less kidney-focused perspective because pathogenesis and therapeutic targets localize outside the kidney. As an exception, the upcoming complement inhibitors are an exciting tool to control glomerular injury locally. Furthermore, an increasing number of drugs targeting non-immune mechanisms of GN chronicity will improve patient outcomes across all GN disease entities. Therefore, the GN-AC matrix proposed here may help focusing on clinically relevant aspects and bypassing some of the existing hurdles in GN teaching, research, and management.

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