JCI The Journal of Clinical Investigation

Interstitial nephritis: another kissing disease?

Eric G. Neilson

J Clin Invest. 1999;104(12):1671-1672. https://doi.org/10.1172/JCI7944.

Commentary

Over the last few decades, nephrology has made great progress in explaining the mechanisms of interstitial nephritis. Such headway comes from 2 general lines of investigation. First has been the notion that cellular immunity is the principal effector of interstitial injury (1), and second has been the idea that interstitial nephritis is the final common pathway to renal failure (2). This latter belief has prompted new work on the cell biology of renal progression. Now the report by Becker et al. in this issue of the JCI (3) introduces a third observation and a new wrinkle: Epstein-Barr virus (EBV) may be the root cause for most idiopathic interstitial disease. The renal interstitium comprises the virtual spaces surrounding glomeruli and their downstream tubular nephrons. These intertubular regions are home to resident and trafficking cells such as fibroblasts, dendritic cells, occasional lymphocytes, and lipid-laden macrophages. The vasa rectae, which siphon off solute and water following tubular reclamation of glomerular filtrate, are also part of the interstitium, as is the web of connective tissue that supports the kidney's emblematic architecture of tubules folded upon themselves. The relational precision of these structures determines the unique physiology of this complex organ. Although interstitial nephritis can be a primary cause of renal failure, it usually follows glomerular injury from antibody-mediated diseases, the endocrine and pressure disturbances […]

Interstitial nephritis: another kissing disease?

Commentary

See related article, pages 1673–1681.

Eric G. Neilson

Division of Nephrology and Hypertension, Departments of Medicine and Cell Biology, Vanderbilt University Medical Center, D-3100 Medical Center North, Nashville, Tennessee 37232, USA. Phone: (615) 322-3146; Fax: (615) 343-9391; E-mail: eric.neilson@mcmail.vanderbilt.edu.

Over the last few decades, nephrology has made great progress in explaining the mechanisms of interstitial nephritis. Such headway comes from 2 general lines of investigation. First has been the notion that cellular immunity is the principal effector of interstitial injury (1), and second has been the idea that interstitial nephritis is the final common pathway to renal failure (2). This latter belief has prompted new work on the cell biology of renal progression. Now the report by Becker et al. in this issue of the *JCI* (3) introduces a third observation and a new wrinkle: Epstein-Barr virus (EBV) may be the root cause for most idiopathic interstitial disease.

The renal interstitium comprises the virtual spaces surrounding glomeruli and their downstream tubular nephrons. These intertubular regions are home to resident and trafficking cells such as fibroblasts, dendritic cells, occasional lymphocytes, and lipid-laden macrophages. The vasa rectae, which siphon off solute and water following tubular reclamation of glomerular filtrate, are also part of the interstitium, as is the web of connective tissue that supports the kidney's emblematic architecture of tubules folded upon themselves. The relational precision of these structures determines the unique physiology of this complex organ.

Although interstitial nephritis can be a primary cause of renal failure, it usually follows glomerular injury from antibody-mediated diseases, the endocrine and pressure disturbances of hypertension, or the metabolic consequences of diabetes or atherosclerosis. Glomerular injury probably initiates secondary interstitial disease as a downstream consequence of persistent proteinuria and cytokinuria from leaky glomeruli (4). Regardless of etiology, the interstitial changes are characteristic and include macrophage accumulation, mononuclear inflammation, proteolysis, and tubular atrophy with concomitant fibrosis (5).

The relationship between the tubulointerstitium and the immune system has evolved dramatically as species have become more complex. Tubular nephrons in aglomerular bony fish are immersed in interstitial lymphopoietic tissue full of macrophages and lymphocytes that are part of a primitive immune system (6, 7). In seemingly blissful tolerance, the nephrons operate unperturbed within this monocytic enclave, undoubtedly employing the cleansing properties of a phagocytic environment to better excrete aquatic waste. Further up the evolutionary tree, in land mammals such as rodents and primates, there is devolution of the interstitium away from its close interdependence on lymphoid tissue. This separation may reflect the need in mammals to develop osmotic gradients that are inhospitable for lymphopoiesis, as well as the kidney's more recessed and protective isolation behind peristaltic ureters. When interstitial inflammation occurs in metanephric kidney, immune attack is spearheaded by mononuclear cells returning from the periphery (1). The extent of tubulointerstitial injury depends on the degree of lymphocyte attraction and the relative antigen-presenting properties of interstitial dendritic cells or renal epithelium (1, 8). The inflammatory consequences are surprisingly complex, given the rather monotonous histologic look of this pernicious lesion.

The causes of primary interstitial nephritis fall into 3 broad categories: (a) the development of nephritogenic autoimmunity following the loss of tolerance to parenchymal-self; (b) the administration of nephritogenic pharmaceuticals; and (c) exposure to a variety of infectious agents (2). The transition from acute to chronic interstitial disease with the onset of tubular atrophy and fibrosis can be as short as a few weeks. If inciting events are not dealt with quickly, the kidneys will fail.

Interstitial nephritis following infection, particularly from bacteria such as streptococci or diphtheria, was first described by Councilman over 100 years ago (9). Today, these infections occasionally produce interstitial injury in children. Sporadic reports of infectious interstitial nephritis in adults favor the odd bacteria, exotica like *Rickettsia*, *Leptospira*, or *Schistosoma mekongi*, and viruses such as HIV and Hantaan virus, to name a few (2). Up to now, there has been no predictive consistency for producing interstitial nephritis by any microbe, and this is why Becker's report generates fresh excitement (3). This group provides the surprising observation that patients with primary and persistent interstitial nephritis unrelated to drugs or acute infection — that is, seemingly idiopathic — had EBV genomes expressed exclusively among proximal tubular epithelia in 9 of 9 random biopsies taken over 8 years. This well-controlled finding is intriguing for its consistency and provocative for advancing viruses as an etiology.

If one were to pick a virus with staying power and a quirk for pathologic mischievousness, a herpesvirus like EBV would be a good choice.

EBV is a ubiquitous herpesvirus that can persist in a latent form, usually within a small fraction of B lymphocytes that are not removed by the immune response following primary infection. Primary infection of oropharyngeal epithelium and B cells via

the CD21(CR2) receptor is asymptomatic in small children and is associated with mononucleosis in adolescence. Later in life, EBV may reawaken as asymptomatic viremia, spontaneous lymphoid malignancy, or, at any age, as a lymphoproliferative disorder following immunosuppression (10). Some children with AIDS and EBV also develop smooth muscle tumors, suggesting that nonlymphoid cells can be a nidus for reanimating proliferative diseases. The variations in EBV-associated malignancy may relate to one of several recognized forms of viral latency (10).

If most of the population carries EBV, why is primary ideopathic interstitial nephritis so uncommon? The explanation is not obvious. Becker's group observed that CD21 receptors were expressed constitutively and exclusively along the proximal tubules of normal kidney (3), so viral entry into somatic cells due to the selective appearance of new receptors seems unlikely. Perhaps those who develop EBV-related interstitial nephritis are infected secondarily with a close cousin of EBV that is not distinguishable by current probes, or manifest a new CD21 ligand that reawakens latent EBV in tubular epithelium, or have a nephritogenic viral polymorphism that favors a previously unrecognized form of viral latency, or express a genetic polymorphism that is MHC-restricted for EBV epitopes and focuses an immunologic cross-reactivity to interstitial antigens. At the moment, there are many hypotheses but few answers.

What is it about persistent EBV that encourages inflammation? Latency produces at least 9 viral proteins — particularly the EBV nuclear antigens (EBNAs) and the latent membrane proteins (LMPs) — some of which can be autoimmune (11). On the other hand, some EBV-infected cells express vIL-10, which blocks B7 costimulation of antigen-reactive T lymphocytes (12), perhaps creating a state of immunologic privilege. Furthermore, binding of EBV to its CD21 receptor can signal NF-κB during self-limited primary infection (13).

More important, perhaps, is the constitutive expression of LMP1 during latency. This TNF-like receptor induces the apoptosis-protective protein bcl-2 (14) and also triggers cytoplasmic IκB release from NF-κB so that NF-κB can move to the nucleus (15; see also the Perspective by Sellers and Fisher in this issue). In the nucleus, NF-κB reawakens the transcription of numerous proinflammatory genes that, in the proper context, could facilitate interstitial injury. Monocyte attracting chemokines (MIP-1, MCP-1), cell adhesion molecules (ICAM, VCAM), TNF-α, and the profibrotic moieties angiotensinogen, transglutaminase, osteopontin, and FSP-1, to name a few (16), are all relevant effectors of interstitial injury. Both TNF-α and angiotensin II trigger more NF-κB release (16), and a vicious circle of monocytic infiltration (17), epithelial-mesenchymal transformation (18), and interstitial fibrosis may ensue (19, 20).

The novel findings of Becker et al. remind us how important serendipity is to discovery. If one were to pick a virus with staying power and a quirk for pathologic mischievousness, a herpesvirus like EBV would be a good choice. The strength of present findings invites confirmatory work. A new door has opened to the understanding of interstitial nephritis. Ahead lies unanticipated opportunity and a fresh approach to viral-mediated renal pathology.

1. Kelly, C.J. 1999. Cellular immunity and the tubulointerstitium. *Semin. Nephrol.* **19**:182–187.
2. Kelly, C.J., and Neilson, E.G. 1996. Tubulointerstitial diseases. In *The kidney*. B. Brenner and F. Rector, editors. W.B. Saunders Co. Philadelphia, PA. 1655–1679.
3. Becker, J., et al. 1999. Epstein-Barr virus infection of renal proximal tubule cells: possible role in chronic interstitial nephritis. *J. Clin. Invest.* **104**:1673–1681.
4. Remuzzi, G., and Bertani, T. 1998. Mechanisms of disease: pathophysiology of progressive nephropathies. *N. Engl. J. Med.* **339**:1448–1456.
5. Neilson, E.G. 1989. Pathogenesis and therapy of interstitial nephritis. *Kidney Int.* **35**:1257–1270.
6. Forster, R. 1975. Structure and function of aglomerular kidneys. *Fortschr. Zool.* **23**:232–247.
7. Tadashi, T. 1988. The role of renal macrophages in the aglomerular kidney of the sea-horse (teleost) in the removal of exogenous macromolecules from circulating blood. *Arch. Histol. Cytol.* **51**:327–339.
8. Wuthrich, R., Singer, G., and Rubin-Kelley, V. 1997. Antigen presentation by renal parenchyma. In *Immunologic renal diseases*. E. Neilson and W. Couser, editors. Lippincott-Raven Publishers. Philadelphia, PA. 193–202.
9. Councilman, W.T. 1898. Acute interstitial nephritis. *J. Exp. Med.* **3**:393–408.
10. Liebowitz, D., and Kieff, E. 1993. Epstein-Barr virus. In *The human herpesviruses*. B. Roizman, R. Whitley, and C. Lopez, editors. Raven Press. New York, NY. 107–172.
11. Dreyfus, D., Kelleher, C., Jones, J., and Gelfand, E. 1996. Epstein-Barr virus infection of T cells: implications for altered T-lymphocyte activation, repertoire development and autoimmunity. *Immunol. Rev.* **152**:89–110.
12. Muller, A., Schmitt, L., Raftery, M., and Schonrich, G. 1998. Paralysis of B7 co-stimulation through the effect of viral IL-10 on T cells as a mechanism of local tolerance induction. *Eur. J. Immunol.* **28**:3488–3498.
13. Sugano, N., Chen, W., Roberts, M., and Cooper, N. 1997. Epstein-Barr virus binding to CD21 activates the initial viral promoter via NF-κB induction. *J. Exp. Med.* **186**:731–737.
14. Henderson, S., et al. 1991. Induction of bcl-2 expression by Epstein-Barr virus latent membrane protein 1 protects infected B cells from programmed cell death. *Cell.* **65**:1107–1115.
15. Sylla, B., et al. 1998. Epstein-Barr virus-transforming protein latent infection membrane protein 1 activates transcription factor NF-κB through a pathway that includes the NF-κB-inducing kinase and IκB kinases IKKα and IKKβ. *Proc. Natl. Acad. Sci. USA.* **95**:10106–10111.
16. Klahr, S., and Morrissey, J. 1998. The role of growth factors, cytokines, and vasoactive compounds in obstructive nephropathy. *Semin. Nephrol.* **18**:622–632.
17. Morrissey, J., and Klahr, S. 1998. Enalapril decreases nuclear factor kB activation in the kidney with ureteral obstruction. *Kidney Int.* **52**:926–933.
18. Strutz, F., et al. 1995. Identification and characterization of a fibroblast marker: FSP1. *J. Cell Biol.* **130**:393–405.
19. Eddy, A. 1996. Molecular insights into renal interstitial fibrosis. *J. Am. Soc. Nephrol.* **7**:2495–2508.
20. Okada, H., Strutz, F., Danoff, T.M., Kalluri, R., and Neilson, E.G. 1996. Possible mechanisms of renal fibrosis. *Contrib. Nephrol.* **118**:147–154.