


In this issue of the Journal of the American Society of Nephrology, Nickeleit et al.3 put forward a classification of polyomavirus nephropathy (PVN) that combines clinical and pathologic features to generate a working definition of “definitive polyomavirus nephropathy.” More importantly, they have shown that, across the three severity classes of PVN, there is a progressively worse renal prognosis at 12 and 24 months.3

The number of known human polyomaviruses has now reached 15, of which only four are known to be pathogenic to humans: BKV (BKPyV), JCV (JCpyV), Merkel cell PyV, and trichodysplasia-spinulosa-associated PyV.4,5 Primary infection with BKV and JCV occurs in childhood, and these viruses commonly establish latency in the urinary tract, emerging under immunosuppression.6–8 After kidney transplant, there commonly occurs activation of latent polyomavirus, chiefly BKV but to a much lesser extent, JCV,9 in the kidney and lower urinary tract, particularly in association with higher levels of immunosuppression. A recent report of the virome in patients with kidney transplants suggests considerable complexity among PV genomes as well as reports the finding of the genome of torcetaren virus, a widely distributed virus of uncertain pathogenicity.8 At present, overt PVN occurs in about one third of kidney transplant recipients. The diagnosis of PVN may be made on clinical grounds, as presumptive PVN, with falling renal function and high or rising BKV virus titers, or by kidney biopsy.

The Banff classification of PVN, proposed in this issue by Nickeleit et al.,3 was developed using 192 kidney biopsies available to the working group, all from subjects with biopsy-proven PVN. In the majority of patients, the clinical diagnosis made at the time of the renal biopsy was acute allograft rejection. The presence of BKV was shown by intranuclear inclusions on electron microscopy (81%) or immunostaining for the T antigen (19%). The objective was to identify factors that would predict loss of allograft function over the ensuing 24 months.

The authors used a mixed effect model repeated measurement approach, applying forward selection to identify factors associated with allograft function. The two variables in the final model included (1) polyomavirus replication/load level determined in a semiquantitative fashion from zero to three on the basis of determining the fraction of tubules with morphologic evidence of polyomavirus replication (particularly as shown by SV40 antibody staining) and (2) the Banff interstitial fibrosis (chronic injury) scores from zero to three, representing no, mild, moderate, and severe fibrosis, respectively.10 The six groups thus defined were collapsed into three classes on the basis of clinical outcomes and excluding patients with acute rejection. The authors contend, plausibly, that class 1 likely represents early stages of viral reactivation, with low chronic injury scores, whereas class 2 and class 3 occur somewhat later and represent more advanced disease. The choice of fibrosis rather than inflammation was made on the basis of analyses showing that fibrosis was the more powerful predictor of outcome. One weakness of reducing from six to three categories was that it was carried out on

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**Banff Classification of Polyomavirus Nephropathy: A New Tool for Research and Clinical Practice**

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Over the past two decades, various transplant nephrologists and renal pathologists have worked together under the banner of the Banff Working Group to define aspects of renal disease and renal pathology in the setting of kidney transplantation. Polyomavirus pathology has been a particular area of interest.1,2

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the basis of the entire dataset; although this is understandable given the limited number of patients available, it does run the risk of overfitting the scheme to fit this particular dataset.

As shown in Figure 4 of the paper by Nickeleit et al., the PVN score at the time of the biopsy was predictive of change in creatinine at 12 months and again, at 24 months, with class 1 doing better than class 2 and class 2 doing better than class 3. As shown in their Figure 5, the authors propose a monitoring schema for patients with renal transplants that begins with urinary screening for polyomavirus that is followed, for some patients, with plasma screening for polyomavirus. The finding of BK viral copy numbers >10,000 copies per milliliter, possibly further supported by a positive Haufen test (the finding of viral particle aggregates on electron microscopy; Haufen means heap, cluster, or stack in German), would lead to consideration of a kidney biopsy. The rationale for biopsy would be that the diagnosis of PVN would favor reduction in immunosuppressive therapy.

In conclusion, this new grading scheme for PVN, which incorporates clinical and pathology features, shows significant differences in outcomes among the three tertiles in terms of risk for PVN. Although it will be important to validate this approach with new cohorts, it seems to provide useful prognostic information for clinical care and research applications.

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DISCLOSURES

None.

REFERENCES


Editorial Note: From Both Sides Now

Josephine P. Briggs and Thomas H. Hostetter

I have looked at clouds from both sides now, from up and down.

Joni Mitchell

In this issue of the Journal of the American Society of Nephrology (JASN), the Perspective section features brief essays arguing opposing sides of a tough issue. Baigent and Lennon argue that CARDINAL, the ongoing clinical registration trial of bardoxolone for Alport syndrome (NCT030319185) will not adequately address long-term safety. Toto, a member of the Data Safety Monitoring Board for the CARDINAL, argues that the trial is safe and well justified.

The argument is in part a debate about competing surrogate markers. In the two previous trials of bardoxolone, BEAM and BEACON, the two intermediate measures used to assess possible benefit went in opposite directions: eGFR increased but so did the albumin-to-creatinine ratio (ACR). Nephrologists are generally comfortable with albumin excretion as a