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Diagnosis Including Differential Diagnosis of BKN Nephropathy and Rejection

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Polyomavirus nephropathy (PVN), also commonly termed BK virus nephropathy (BKVN), is a viral infection that impacts up to 15% of kidney allografts and results in graft loss in up to 50% of those affected. The diagnosis of BKVN is either presumptive, based on the number of plasma viral copy numbers often determined as >10,000 copies/mL present for 3 or 4 weeks, or proven, requiring replicating virus in a kidney biopsy identified by immunohistochemistry (IHC). The virus is seen in tubular epithelial cell nuclei, favoring distal tubules and collecting ducts, and infrequently in glomerular parietal epithelium. Other histologic features of BKVN include tubular cell viral cytopathic changes, necrosis of tubular cells which may or may not be infected, sharply demarcated geographic inflammation, and a mixed tubulointerstitial inflammatory infiltrate which may be plasma cell rich. These findings should prompt a careful search for BKV using IHC against the SV40 large T antigen, although BKV may be present with no inflammation or tubular cell abnormalities. A subset of cases will have tubular basement membrane immune complex deposits containing BKV antigen; the significance of this is unknown. There are some caveats to kidney biopsy findings and IHC staining for the diagnosis of BKVN. The virus preferentially infects medullary tubular structures. When both cortex and medulla are sampled, virus is identified in up to 58% of cases and seen only in the medulla in approximately 10% of cases. When only cortex is sampled the BKV identification rate may fall to 24%. In up to 40% of biopsies with two tissue cores from cortex and/or medulla, BKV staining will be discordant in the cores. BKV inclusions are seen less often in very early and late disease, and when infection has resolved. The false negative rate for BKV IHC may be reduced to less than 10% if kidney biopsy is performed when the plasma viral load is >1 million copies/mL, if kidney function has declined by >20% in the setting of plasma virus, if there are viral noncoding control region (NCCR) gene rearrangements identified in virus in the plasma, or if Haufen are identified in the urine. Haufen are urinary aggregates of viral DNA that can be identified by electron microscopy. Importantly, JC virus will stain positively by IHC for SV40 but with no plasma BKV DNA. In this case, testing should be done for JC virus. There have been several PVN/BKVN histologic classification schemes proposed over the last 20 years. A classification scheme should encompass the clinical presentation at time of biopsy, and the

subsequent risk of declining kidney function and graft failure. The incorporated histologic features include the extent of tubular cell infection, degree of parenchymal scarring and possibly the severity of tubulointerstitial inflammation. An initial classification was proposed by Drachenberg at the U of Maryland and modified by the American Society of Transplantation (UMD), and a working classification also was proposed by Banff. Both used Classes A, B and C with UMD subdividing Class B into B1, B2 and B3 depending on the extent of tubular injury and parenchymal inflammation. The classifications differed with respect to inflammation and tubular injury, with UMD Class A having no or minor inflammation with any tubular injury but Banff Class A allowing any inflammation but no or minimal tubular injury. There were differences in Class B as well although Class C was similar, requiring >50% interstitial fibrosis with any degree of tubular injury. These classifications were assessed for their clinical relevance and Class C consistently was associated with more graft loss in both schemes. However, many of the Banff Class A biopsies corresponded to Class B in the UMD classification. It was determined that the Classes were too overlapping and broad, and had inconsistent feature correlation with outcome. Therefore, the Banff polyomavirus working group proposed a new classification based on the percentage of tubules with infected cells and the Banff ci score of interstitial fibrosis. The degree of inflammation was not included as it was not consistently identified in active infection. The current Banff classification includes Class 1 with < 25% fibrosis and <1% infected tubules, Class 2 with <1% infected tubules and >25% fibrosis or 1-10% infected tubules with any fibrosis or >10% infected tubules with < 25% fibrosis, and Class 3 with >10% infected tubules and >25% fibrosis. In assessing the clinical relevance of this Banff classification, some studies found significant correlations between Classes 1-3 and the serum creatinine level 24 months after biopsy while others did not, although Class 3 consistently had the worst outcome. Classes 1 and 2 also fared significantly better following viral clearance and disease resolution, with clearance associated with more graft survival. However, in early disease there may be poor correlations with subsequent viral clearance, kidney function or graft failure. There are some histologic features that correspond to resolving infection which may impact biopsy interpretation. As the virus clears, usually with reduced immunosuppression, there initially may be more tubulointerstitial inflammation and plasma cells likely reflecting a type of immune reconstitution. This may be associated with a transient rise in the serum creatinine level without increased atrophy or fibrosis. It has been shown that with reduced immunosuppression, viral clearance often occurs 2-4 months after biopsy. Repeat biopsy at the end of this period may predict prognosis with a worse outcome if there is increased tubulitis, more extensive fibrosis or rejection. Transplant rejection may occur preceding, concurrent with or following BKN, and it may be difficult to differentiate these disparate forms of transplant kidney injury. Some kidney biopsy histologic features that are helpful in this regard include tubular cell viral inclusions, very geographic inflammation which often is more medullary, and more plasma cells and neutrophils in BKVN. In contrast, in acute rejection there tends to be diffuse and more severe tubulitis without BKV inclusions, more eosinophils, arterial inflammation, glomerulitis, transplant glomerulopathy and peritubular capillary C4d staining. When cell-mediated rejection and BKN co-occur, tubulitis more than a 20x field away from any viral inclusions has been suggested as indicating rejection. MCH

class II (HLA-DR) has been reported variably to occur only with rejection but also with BKVN, so is not useful in this setting. The types of urine and graft infiltrating cells have been evaluated as a means to distinguish rejection from BKVN. Rejection episodes are associated with urinary CD4+ and CD8+ T and effector memory T cells and with increased CD8+ cortical T cells. In contrast, more medullary CD20+ cells are present in BKVN. Molecular diagnostics have been applied to this dilemma. Diagnostic gene sets may be of ancillary help in making a diagnosis of BKVN, but to date have not been able to consistently differentiate BKVN from rejection. In summary, BKVN can be diagnosed presumptively by blood viral DNA and proven by allograft biopsy with the caveat that the virus is focally in the tissue and may not be in a tissue sample. There are BKVN histologic classifications, which correlate with clinical outcomes to some extent. Repeat biopsy at 3-4 months with evaluation in the context of viral clearance or disease persistence is useful for prognostication. Differentiating cell mediated rejection in the setting of concurrent or recently treated BKVN is difficult, although there are some suggestive morphologic, immunologic and molecular findings. However, work remains to be done to develop methods for definitely distinguishing rejection and BKVN, to ensure appropriate therapy and optimal outcomes for kidney transplant recipients who contract this challenging viral infection.