Kidney allograft interstitial fibrosis and tubular atrophy-IFTA due to specific causes: Polyomavirus nephropathy.

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Chronic fibrosing changes of the kidney graft parenchyma constitute the most difficult challenge in the field of kidney transplantation. In the previous issue of this journal, we discussed the diagnostic aspects of bacterial infections causing chronic changes of the graft parenchyma. In this tutorial, which is mainly pictorial, we discuss another common infectious cause of chronic graft changes and graft loss, i.e., polyomavirus nephropathy (PVN).

Polyomavirus nephropathy (PVN) is defined as an intragraft / intraparenchymal, productive polyomavirus infection involving the medulla and/or cortex of the kidney with morphologic and/or immunohistochemical and/or molecular evidence of viral replication in the form of in-situ hybridization associated with varying degrees of parenchymal damage ranging from minimal to marked, and accompanied by inflammation and fibrosis.

PVN is a common viral infection of kidney allografts, with biopsy-proven incidence of approximately 5% worldwide.

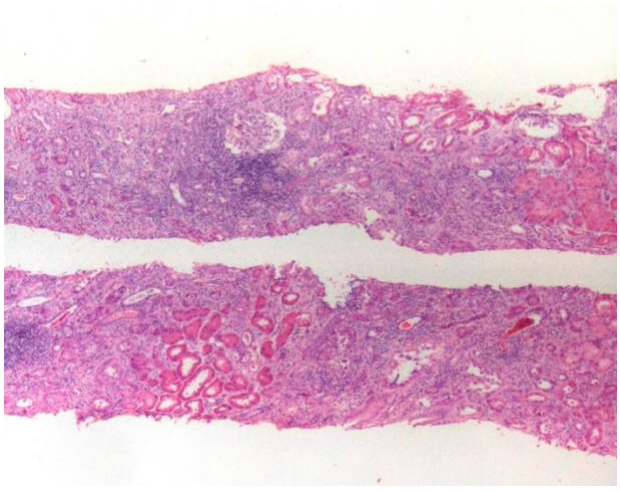

Figure 1. Two cores of an adequate kidney graft biopsy comprising of cortex in these fields. Elsewhere medulla was also present. Please note that medulla is required for diagnosis of early stage of PVN. There is dense inflammatory cell infiltration and marked tubular atrophy. It is difficult to discern the cause of inflammation at this magnification. (H&E, ×50).

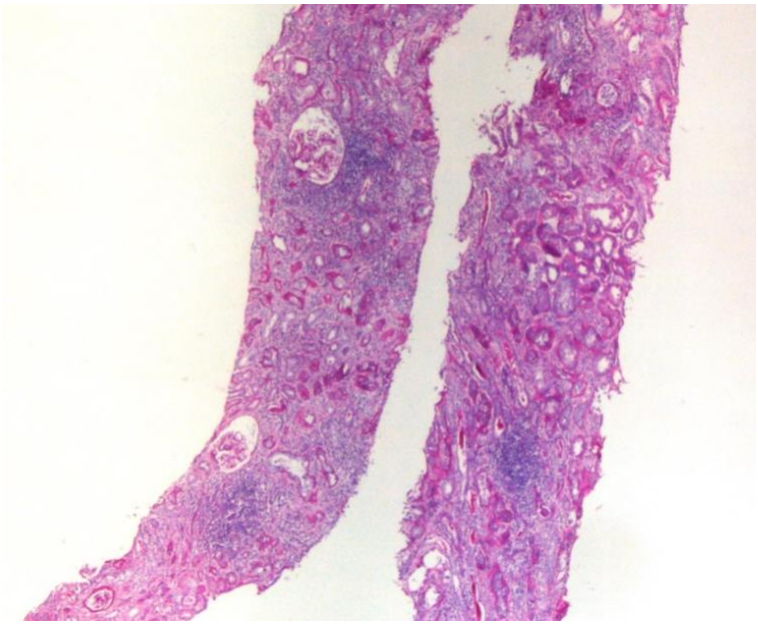

Figure 2. Another representative area of the two cores of kidney graft biopsy shown in Figure 1 comprising mostly of cortex with beginning of medulla in one core at one edge. There is dense inflammatory cell infiltration with formation of lymphoid nodules and marked tubular atrophy. As in previous biopsy, it is not possible to discern the cause of inflammation at this magnification. (H&E, ×50).

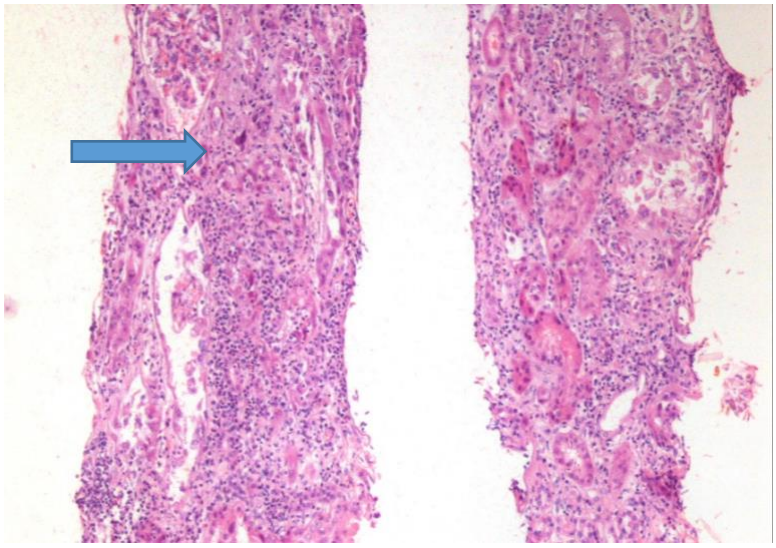

Figure 3. The same two cores of kidney graft biopsy at slightly higher magnification as compared with Figures 1 and 2. In the background of moderate interstitial inflammation, some tubular epithelial cell nuclei appear enlarged and hyperchromatic (arrow). Such a finding raises the suspicion of some viral cytopathic effects and needs examination at high magnification and confirmation by ancillary techniques. (H&E, ×100).

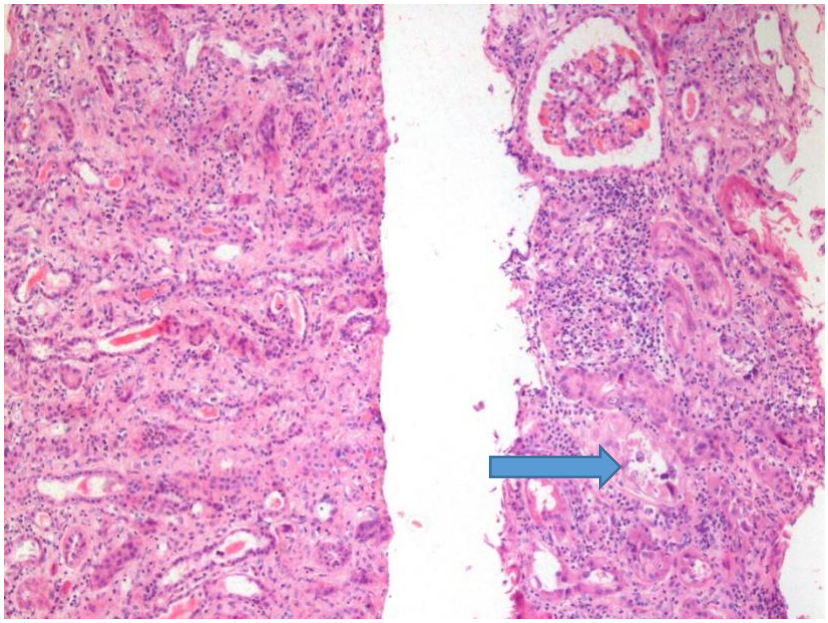

Figure 4. Another representative area of the same two cores of kidney graft biopsy at slightly higher magnification as compared with Figures 1 and 2. In the background of moderate interstitial inflammation and moderate tubular atrophy, some tubular epithelial cell nuclei appear enlarged and hyperchromatic (arrow). Such a finding raises the suspicion of some viral cytopathic effects and needs examination at high magnification and ancillary techniques. One glomerulus included in the field shows no significant pathology (H&E, ×100).

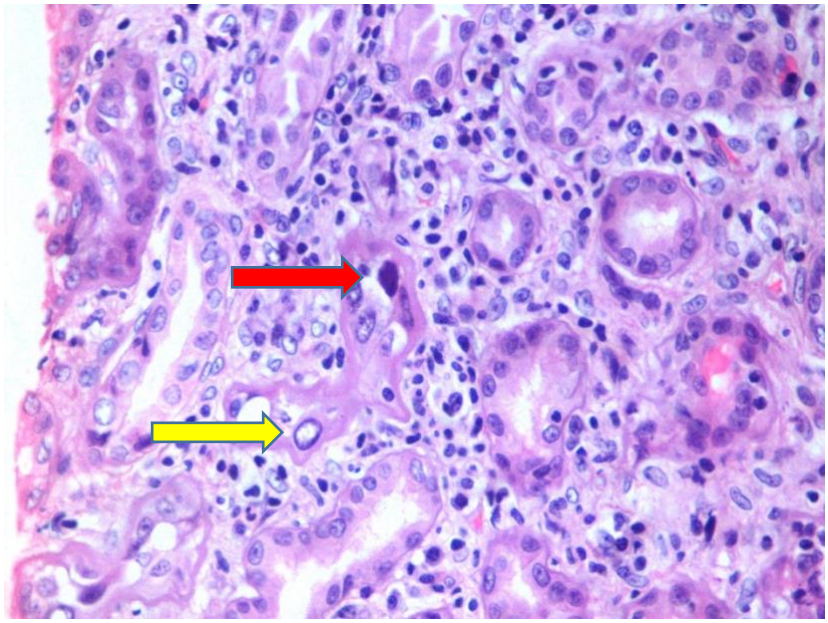

Figure 5. A representative area of one of the two cores of kidney graft biopsy at medium-power magnification. In the background of moderate interstitial inflammation and mild tubular atrophy, one tubular cross-section shows at least two epithelial cell nuclei, one with a smudged chromatin pattern (red arrow) and another one with optical clearing (yellow arrow). Such changes indicate productive viral replication and cytopathic effects on light microscopy. (H&E, ×200).

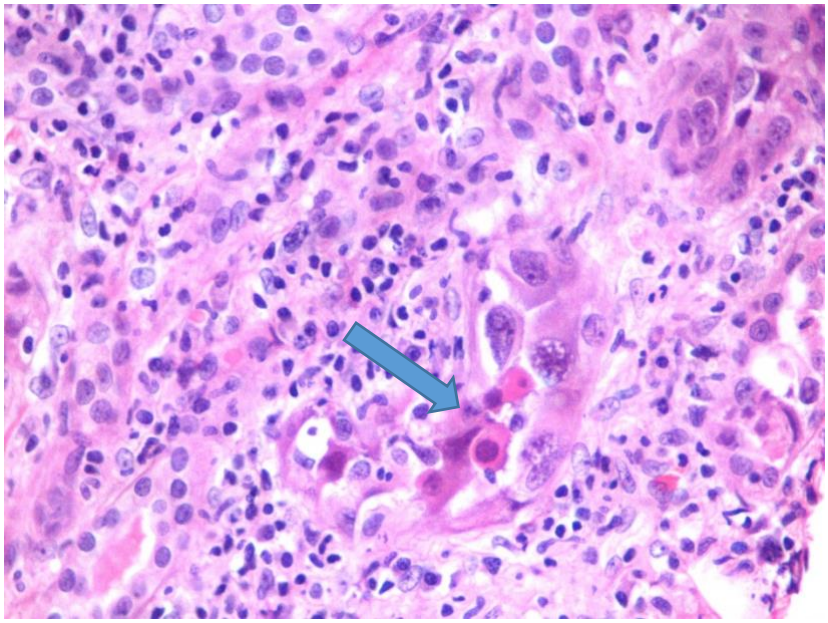

Figure 6. Another representative area of one of the two cores of kidney graft biopsy at high-power magnification. In the background of moderate interstitial mixed inflammatory cell infiltration with predominant neutrophils, one tubular cross-section (green arrow) shows many epithelial cells with viral cytopathic effects, including denudation of epithelial cells and cellular degenerative changes. Note that the number of cells with viral intranuclear inclusions is not considered for classification of PVN. (H&E, ×400).

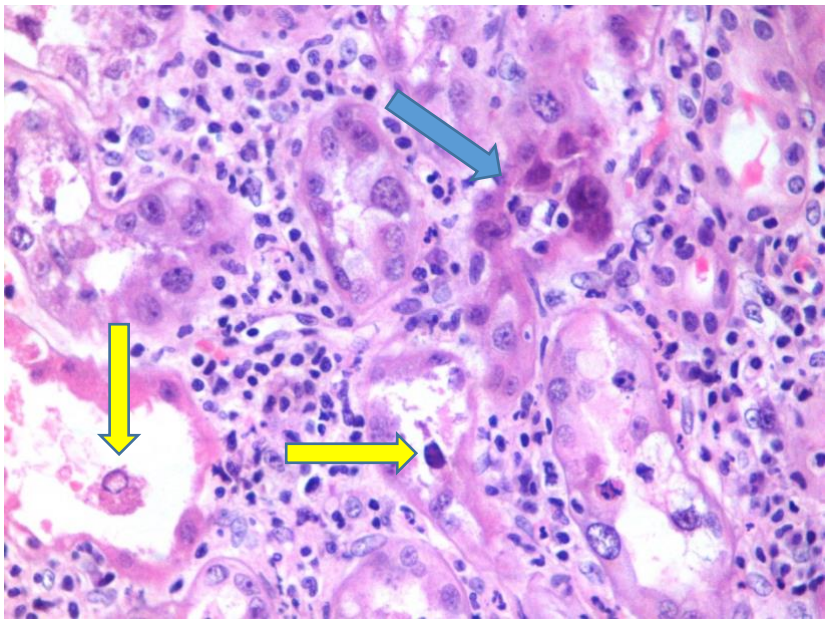

Figure 7. Another area of one of the two cores of kidney graft biopsy at high-power magnification. In the background of moderate interstitial mixed inflammatory cell infiltration with predominant neutrophils, one tubular cross-section (green arrow) shows many epithelial cells with nucleomegaly and smudged chromatin pattern suggestive of viral cytopathic effects. Another two tubules show shed tubular epithelial cells with viral cytopathic effects (yellow arrows). Remaining tubular epithelial cell nuclei show regenerative nuclear enlargement (H&E, ×400).

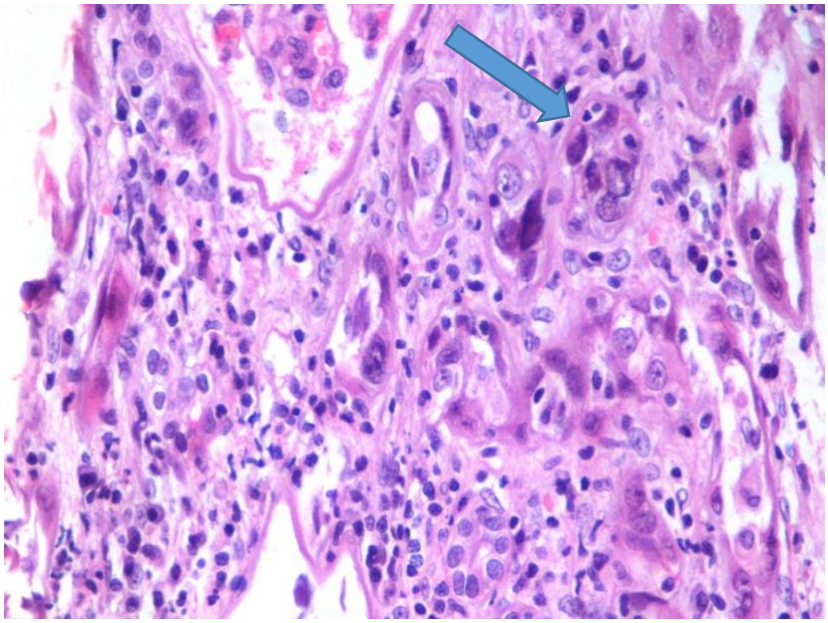

Figure 8. Another area of one of the two cores of kidney graft biopsy at high-power magnification. A number of tubules are showing viral cytopathic effects. One of the tubule is also showing lymphocytic tubulitis (green arrow). (H&E, ×400).

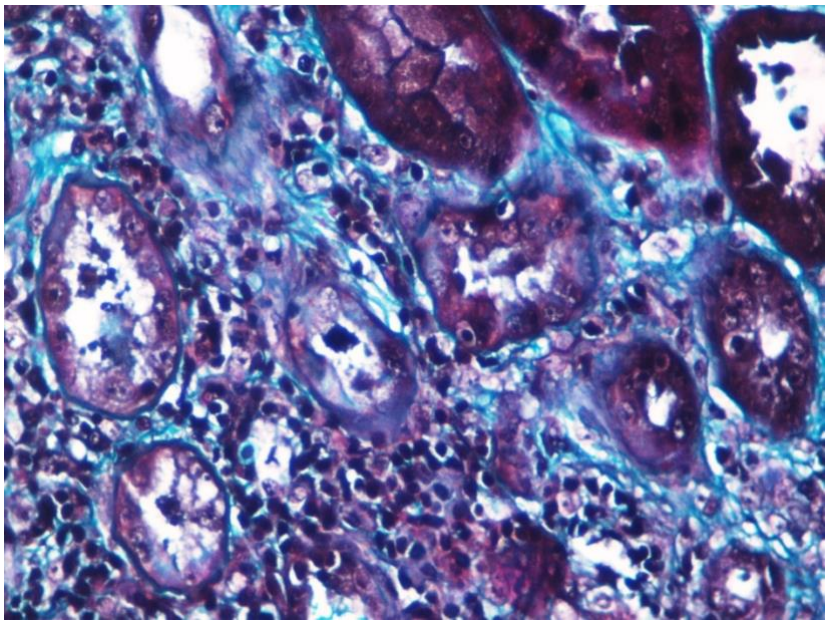

Figure 9. A representative area of one of the two cores of kidney graft biopsy at high-power magnification. In the background of interstitial inflammation, there is mild interstitial fibrosis (ci). This lesion along with viral load is used for classifying PVN according to the Banff classification (Trichrome stain, ×400).

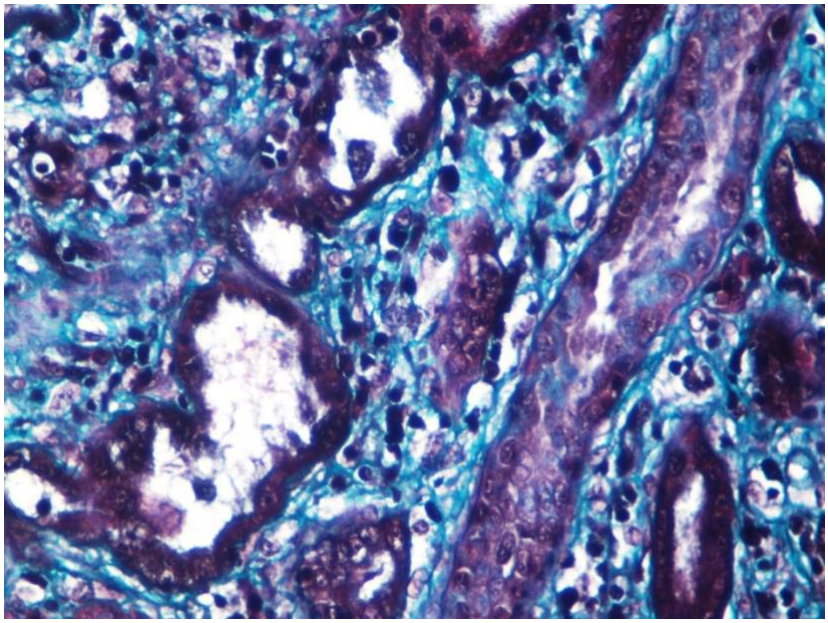

Figure 10. Another representative area of one of the two cores of kidney graft biopsy at high-power magnification. In this particular field, the inflammation is mild, but interstitial fibrosis (ci) is more as seen with green color in this stain. This lesion along with viral load is used for classifying PVN according to the Banff classification. Note that interstitial inflammation is not used for classifying PVN. (Trichrome stain, ×400).

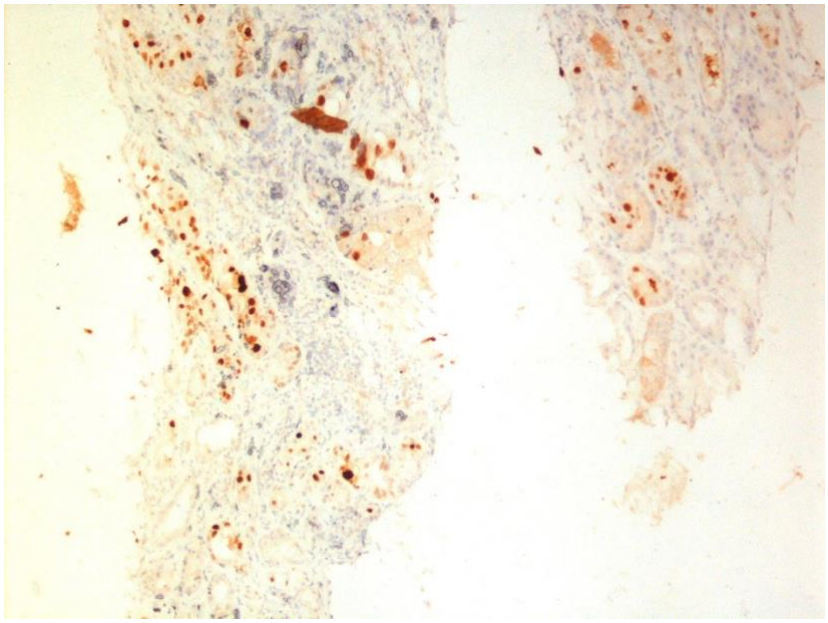

Figure 11. A representative area of the two cores of kidney graft biopsy at low magnification stained for SV40-large T antigen. Many epithelial cells demonstrate crisp intranuclear expression of SV40-T antigen (staining intensity "4-5" on a scale of "0-5"). (IHC for SV40-T antigen, ×100).

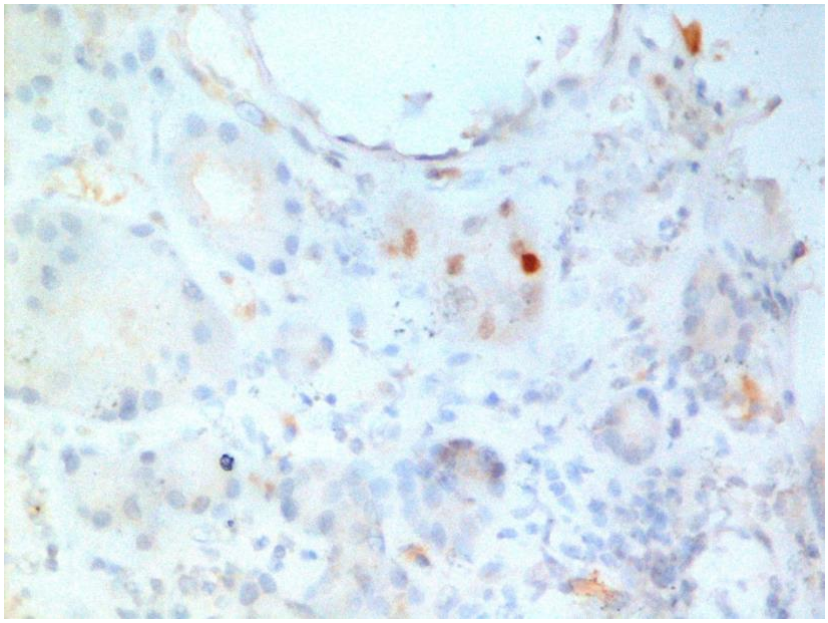

Figure 12. A representative area of the two cores of kidney graft biopsy at medium-power magnification stained for SV40-large T antigen. One tubular cross-section is exhibiting one epithelial cell nucleus with crisp intranuclear expression of SV40-T antigen (staining intensity "4-5" on a scale of "0-5"). Note that the number of cells with viral intranuclear inclusions is not considered for PVN classification. (IHC for SV40-T antigen, ×200).

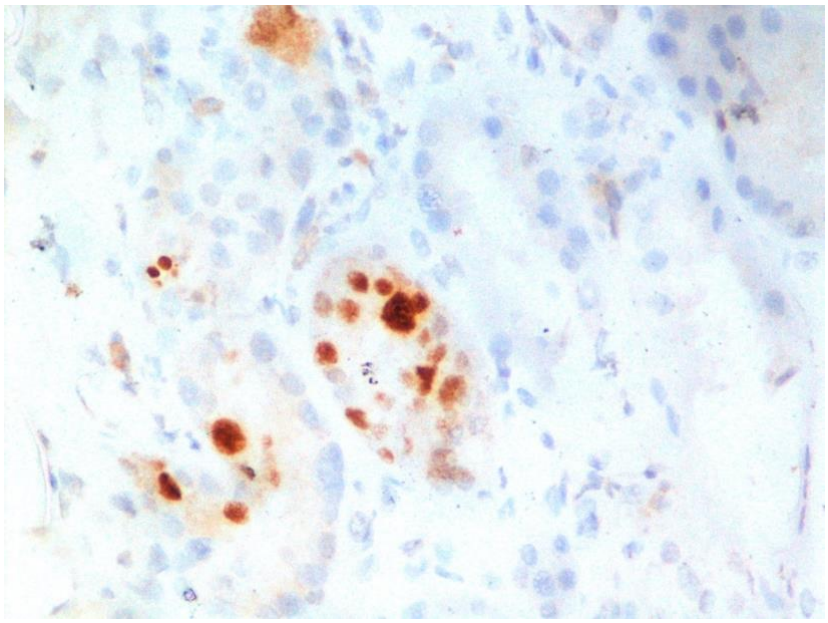

Figure 13. A representative area of the two cores of kidney graft biopsy at medium-power magnification stained for SV40-large T antigen. One of the two tubular cross-sections shows two positive nuclei, while the other shows many positive nuclei. It is the proportion of tubules with viral cytopathic effects that is used for PVN load quantification in PVN classification rather than the number of individual cells per tubule. (IHC for SV40-T antigen, ×200).

Further reading:

1. Nickeleit V, Singh HK, Davis VG, Seshan SV. Classifying Polyomavirus Nephropathy: The "Banff" Initiative. Transpl Int. 2022;35:10299.
2. Nickeleit V, Singh HK, Dadhania D, Cornea V, El-Husseini A, Castellanos A, et al. The 2018 Banff Working Group classification of definitive polyomavirus nephropathy: A multicenter validation study in the modern era. Am J Transplant. 2021;21(2):669-680.
3. Nickeleit V, Singh HK, Randhawa P, Drachenberg CB, Bhatnagar R, Bracamonte E, et al; Banff Working Group on Polyomavirus Nephropathy. The Banff Working Group Classification of Definitive Polyomavirus Nephropathy: Morphologic Definitions and Clinical Correlations. J Am Soc Nephrol. 2018;29(2):680-693.
4. Bouatou Y, Nguyen TQ, Roelofs JJTH, Bemelman FJ, Michielsen L, Goldschmeding R, et al. A Multicenter Application of the 2018 Banff Classification for BK Polyomavirus-associated Nephropathy in Renal Transplantation. Transplantation. 2019;103(12):2692-2700.