BK virus nephropathy, collecting duct cell proliferation and malignancy in a renal allograft: case history and review of the literature

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Case

62yr old female with lithium nephropathy, still on lithium at the time of transplantation

- 2006 pre-emptive renal transplantation (RTX):
  - BK nephropathy 6 months later (viral load 6.4 x 10^6 c/ml)
    - Immunosuppression↓↓
    - Leflunomide
    - Cidofovir
  - Vascular rejection
- Early 2007
  - Serum creatinine stabilized at 250 μmol/L
  - BK viral load decreased but stabilized at 1000 c/ml
- 2010 fatigue, night sweats, fever and weight loss
  - CT scan : renal allograft tumor (fig 1A)
  - Transplantectomy

→collecting duct (CD) carcinoma (fig 1 B-C)

BK Virus (BKV)

Epidemiology

- Prevalence in asymptomatic general population 85%

Clinical presentation in RTX patients

- Tubulo-interstitial nephritis in 5-10%
- Preferential infection of CD cells (Woffian duct-derived)
- Rare carcinomas of Woffian duct-derived epithelia (ureter, pyelum and bladder)
- Extremely rare cases of renal cell carcinoma (n=4)

Oncogenicity

- BKV genome contains Large T Antigen(L-Tag), an "early" T (tumor) antigen
- L-Tag stimulates cell proliferation by inactivating tumor suppressor proteins p53 and pRb
- Immunohistochemical staining for BKV (SV40) specifically stain L-Tag

Hypothesis

- BKV preferably infects epithelia embryonically derived from Wolffian ducts
- BKV induces cell proliferation in these epithelia
- In view of the rarity of BKV induced tumors a second hit is needed to induce malignancy

Results

Proliferating cells in CD tumor are SV40 positive

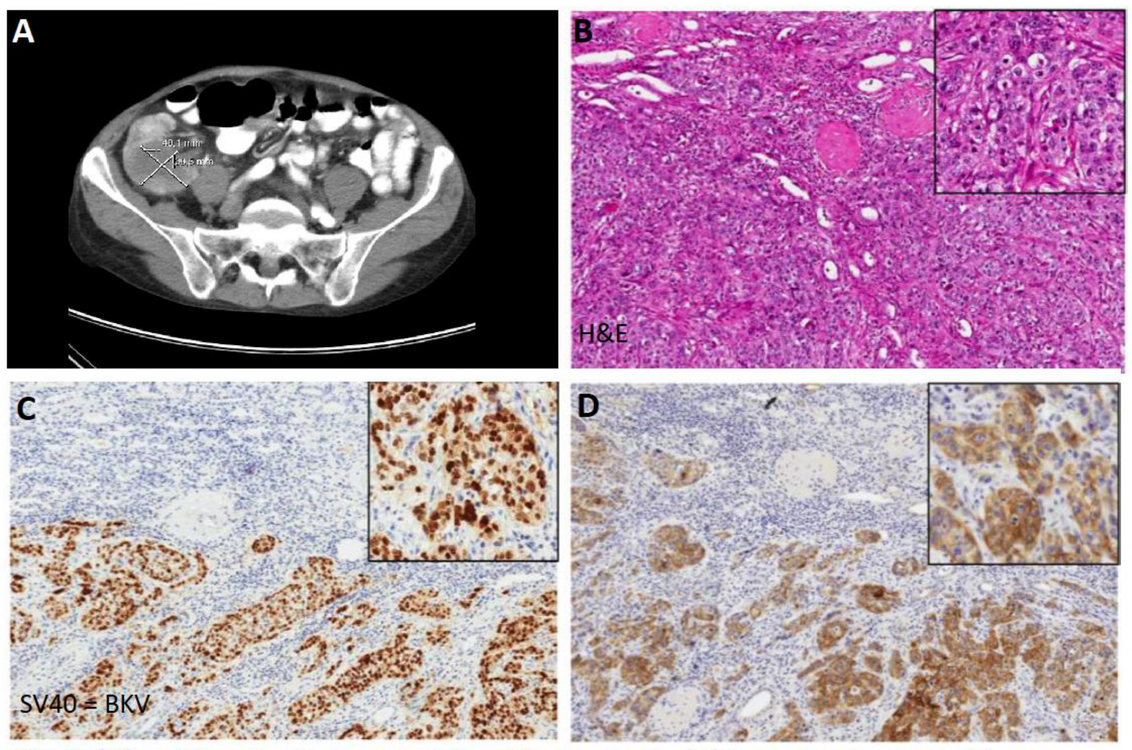

Fig 1. (A) solid mass in upper pole of transplant; (B) tumor cells have bizarre, hyperchromatic nuclei and clear nucleoli, surrounded by clear cytoplasm (H&E); (C) all tumor cells show strong nuclear positivity for SV40 and (D) show co-staining with the CD cell marker "CK-HMW".

BKV (SV40) infects CD cells (CK-HMW) and causes them to proliferate (MIB-1)

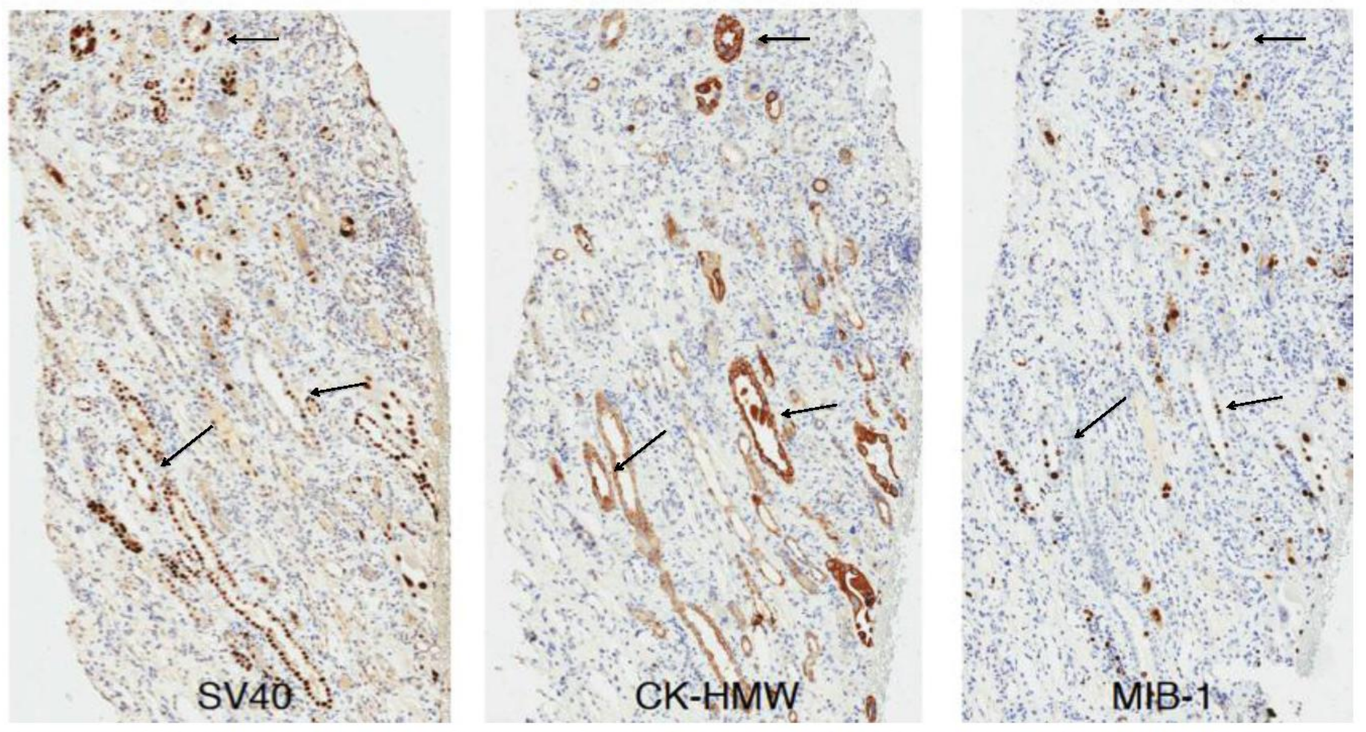

Fig 2. renal biopsy at 9 months after RTX shows, in consecutive slides, extensive BK nephropathy with co-localization of positive tubular segments for SV40, CK-HMW, and the proliferation marker "MIB-1".

Literature review of BKV-associated RTX tumors

	Narayanan [1]	Emerson [2]	Neirynck [3]	Current case
CK7	+	+	+	+
CK19		+	+	+
CK5/6		+		+
CK20	-	-		-
CKHMW				+
E-cadherin				+
N-cadherin				-
SV40	+	+	+	+

Fig 3. Three previous cases of BKV-associated renal allograft carcinomas providing immuno-histochemical typing were SV40 positive and had a profile compatible with a CD origin as in our case.

1.Narayanan M et al., Am J Transplant 2007, 7:1666-1671.
2.Emerson LL et al., Transplant 2008, 12:600-605.
3.Neirynck V et al., Case Rep Nephrol Urol 2012, 2:125-134
4.Rookmaaker MB et al., Clin Kidney J412-415, 2012

Conclusion

- BKV infects CD cells and induces them to proliferate
- As the incidence of BKV infection post RTX is high but the incidence of BKV associated renal allograft tumors is extremely low, an additional proliferative hit is needed for BKV to induce frank tumor formation
- In our case the use of lithium - which also causes CD cell proliferation[4] - at the time of BKV infection may have provided this second hit
- A review of the literature suggests that previously reported cases of BKV-associated allograft carcinomas were also of CD origin

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