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LETTER TO THE EDITOR

Adenoviral graft-nephritis: case report and review of the literature

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Adenovirus is a nonenveloped, double-stranded DNA virus that infects epithelial cells of various organs and causes a wide spectrum of diseases including bronchiolitis, pneumonia, pharyngoconjunctival fever, epidemic conjunctivitis and enteritis [1,2]. In immunocompromised patients such as stem cell (SC) and solid organ transplant recipients, cancer patients who had chemotherapy or radiation, and HIV-infected individuals, systemic disease with lung, liver, and kidney involvement may develop. Amongst transplant patients, SC and intestinal recipients are at the highest risk [3–5]; children seem to be more commonly affected [6]. The virus may be transmitted with the allograft [7]. Type of illness and adenoviral serotype vary according to the underlying disease, patient age and affected organs [8]. Only 20 articles on adenovirus nephritis have been published, most cases developed in SC- and renal transplant (RT) recipients (n = 10) in most cases associated with intensified immunosuppression [9–15]. One RT recipient with adenoviral hepatitis without renal involvement and another with adenoviral hemorrhagic cystitis without nephritis were reported [16,17]. Hemorrhagic cystitis rarely disseminates [18]. Graft nephritis after RT may also be caused by other viruses including polyomavirus (PV), cytomegalovirus (CMV), herpes simplex virus (HSV) and Hantavirus amongst many others, commonly triggered by depleting antibodies such as antithymocyte globulin (ATG), muromonab (OKT3) or alemtuzumab [19–23]. Rituximab is used for treatment of post-transplant lymphoproliferative disorders [24–28], antibody-mediated rejection and preconditioning of patients with high levels of preformed panel reactive antibodies (PRA) [29]. Similar to other depleting agents, this anti-CD20 antibody increases the infection risk [30,31].

Our 27-year-old African American man with focal segmental glomerulosclerosis underwent RT in 2000 and transplant nephrectomy subsequently. He underwent desensitization therapy with plasmapheresis, intravenous immunoglobulin (IVIG), and rituximab, as the PRA level was 53% (antibodies directed against DQ7). PRA levels dropped to <5% and living donated re-RT was performed without complications. Initial immunosuppression included ATG induction, tacrolimus (TAC) with trough levels of 8–12 ng/ml, mycophenolate mofetil (MMF) and

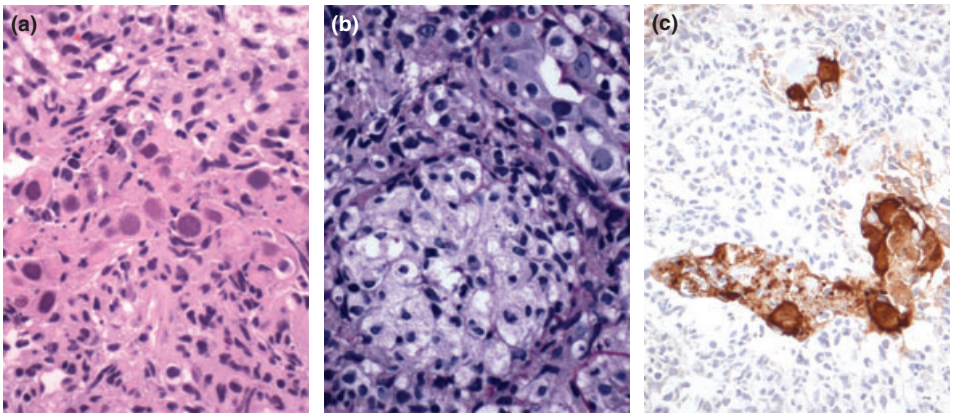

Figure 1 (a) Amphophilic glassy inclusions within enlarged tubular epithelial cell nuclei (H&E ×400). (b) Well-defined interstitial granuloma in a background of severe interstitial inflammation adjacent to affected tubules (PAS ×400). (c) Positive immunohistochemical staining for adenovirus in enlarged tubular epithelial cell nuclei.

Table 1. Data from literature reporting adenovirus nephritis in RT recipients.

Title	First author	Origin	Year	Age/ gender	Risk factor	Affected organ(s)	Time from transplant to nephritis	Attempted therapy	Outcome	Cause of death
Hemorrhagic kidney graft pyelonephritis caused by type 37 adenovirus infection.	Shinohara	Japan	1992	42/F	Renal Transplant	Kidney: pyelonephritis	42 weeks	Alpha interferon	Successful treatment	NA
Adenovirus-induced kidney graft pyelonephritis following renal transplantation	Tomoe	Japan	1994	16/F	Renal Transplant	Kidney	13 months	Antibiotics, IVIG	Successful treatment	NA
Acute adenoviral infection of a graft by serotype 35 following renal transplantation.	Friedrichs	Germany	2003	46/F	Renal transplant	Kidney	29 days	Taper immunosuppression	Successful treatment	NA
Adenovirus Infection of a Renal Allograft	Asim	Qatar	2003	60/M	Renal transplant	Kidney	2 weeks	Decrease CsA, prednisone, MMF	Successful treatment	NA
Adenovirus pyelonephritis in a pediatric renal transplant patient	Kim	Houston, TX	2003	14/F	Renal transplant	Kidney	8 months	Maintainance steroids, cefotaxime	Successful treatment	NA
Adenovirus-associated hemorrhagic cystitis in a pediatric renal transplant recipient	Keswani	Washington, DC	2007	5/M	Renal transplant	Kidney, bladder	68 days	Decrease TAC, discontinued MMF, IV hydration, probenecid, cidofovir	Successful treatment	NA
Adenovirus tubulointerstitial nephritis presenting as a renal allograft space-occupying lesion	Lim	Australia	2007	15/M	Renal transplant	Kidney	36 days	Ganiciclovir, valganiciclovir	Successful treatment	NA
Late-onset acute hemorrhagic necrotizing granulomatous adenovirus tubulointerstitial nephritis in a renal allograft	Alsaad	Canada	2007	19/M	Renal transplant	Kidney	12 years	Cidofovir	Successful treatment	NA
Adenovirus infection of the renal allograft with sparing of pancreas graft function in the recipient of a combined kidney–pancreas transplant	Mathur	Syracuse, NY	1998	30/F	Kidney–pancreas transplant	Kidney	85 days	Taper immunosuppression, immunoglobulins	Successful treatment	NA
Refractory adenovirus infection after simultaneous kidney–pancreas transplantation: successful treatment with intravenous ribavirin and pooled human intravenous immunoglobulin	Emovon	Charleston, SC	2003	46/F	Kidney–pancreas transplant	Kidney, systemic	18 months	Stop TAC and rapamycin, ganiciclovir, CMV hyperimmunglobulin, IVIG, ribavirin	Successful treatment	NA
INDEX case	Hensley	Charlottesville, VA	2008	27/M	Renal transplant	Kidney	6 months	Taper immunosuppression	Successful treatment	NA

Table 2. Data from literature reporting adenovirus nephritis in various clinical settings.

Title	First author	Origin	Year	Age/gender	Risk factor	Affected organ(s)	Time from transplant to nephritis	Attempted therapy	Outcome	Cause of death
Necrotizing tubulointerstitial nephritis associated with adenovirus infection	Ito	Japan	1991	10–69 years, 6M, 4F	Stem cell transplant, Chemotherapy	Kidney, Bladder in all stem cell recipients	37–240 days post-SCT	All autopsy cases; commonly associated with renal failure; 70% also CMV disease	NA	Adenoviral disease together with other infections
Severe adenoviral nephritis following bone marrow transplantation: successful treatment with intravenous ribavirin	Liles	Seattle, WA	1993	25/M	Stem cell transplant	Kidney	81 days	IV ribavirin	Successful treatment	NA
Acute renal failure because of adenovirus-associated obstructive uropathy and necrotizing tubulointersti tial nephritis in a bone marrow transplant recipient	Mori	Japan	2003	17/M	Stem cell transplant	Kidney, Bladder	34 days	Emergency left nephrectomy	Death	Multi organ failure
Adenovirus nephritis in hematopoietic stem cell transplantation	Bruno	Seattle, WA	2004	21 patients; largest published series	Stem cell transplant	Kidney, Systemic	Wide range (weeks to years post-SCT)	Majority diagnosed postmortem, frequently associated with GvHD	High fatality rate	Adenoviral disease in most patients
Successful treatment with oral ribavirin of adenovirus-associated hemophagocytic syndrome in a stem cell transplantation recipient	Iyama	Japan	2005	51/F	Stem cell transplant	Kidney, bladder, hemophagocytic syndrome	nda	Oral ribavirin	Successful treatment	NA
Treatment of adenovirus disease in stem cell transplant recipients with cidofovir	Neofytos	Philadelphia, PA	2007	6 patients: 23/M, 42/F, 39/M, 43/M, 72/M, 33/M	Stem cell transplant	Liver, colon, liver/colon, liver/lungs, colon/liver, kidney/bladder	91 days, 59 days, 68 days, 187 days, 64 days, 214 days	Cidofovir	Alive, alive, died (4 days), alive, died (2 weeks), alive	Fulminant hepatitis, encephalitis
Necrotizing tubulo-interstitial nephritis induced by adenovirus in an AIDS patient	Shintaku	Japan	1993	46/M	HIV	Kidney	nda	Autopsy case; none	Death	CMV, Kapsi, LPD, peritonitis
A case report of adenovirus-related acute interstitial nephritis in a patient with AIDS	Mazoyer	France	2008	34/M	HIV	Kidney	9 years post-HIV infection	IV ribavirin	Death	Invasive aspergillosis
Acute necrotizing tubulointerstitial nephritis because of systemic adenoviral infection	Erdoğan	Turkey	2001	12/F	None	Kidney, liver, brain	NA	Hemodialysis, supportive	Successful treatment	NA
Gross hematuria as a manifestation of membranous nephropathy	Matsukura	Japan	2007	4/F	None	Kidney, membranous nephropathy	NA	Steroids, imidapril, hydrochloride	Successful treatment	NA

nda, no data available.

a steroid taper. The patient was discharged with a serum creatinine of 1.3 mg/dl. Biopsy-proven acute antibody-mediated rejection at 2 months post-RT was successfully treated with another course of rituximab and bolused steroids. Four months later, he was admitted with hematuria and a serum creatinine of 2.4 mg/dl. Urine analysis showed bacteriuria and a positive leukocyte esterase; therefore, ciprofloxacin was started for suspected urinary tract infection. Ultrasound revealed a renal cyst, but normal resistance indices. Allograft biopsy suggested acute antibody-mediated rejection (Banff II^o) and no viral inclusions; immunohistochemical staining for PV and CMV were negative. Serum CMV PCR was negative, as was serology for HSV. Empiric ganciclovir was stopped as CMV PCR remained negative. Repeat biopsy performed 2 weeks later excluded rejection, but revealed numerous enlarged tubular cells with amphophilic glassy nuclear inclusions, highly suspicious for viral tubulitis (Fig. 1a). The tubules demonstrated severe localized damage with associated granuloma formation and severe mixed acute and chronic interstitial inflammation (Fig. 1b). Interstitial hemorrhage was mild. Immunohistochemical staining for CMV, PV, and HSVI, II was negative. Adenovirus was demonstrated by immunohistochemistry at Fred Hutchinson Cancer Research Center (Fig. 1c) and adenovirus serum PCR results returned positive. MRI excluded any vascular complication but revealed mild thickening of the bladder. Cystoscopy with bladder biopsies showed cystitis cystica. MMF was stopped and TAC trough levels lowered to <6 ng/dl, but no antivirals were given. Renal function slowly improved and 2 months later adenovirus was undetectable on serum PCR. Serum creatinine had returned to the baseline level and MMF was restarted. Two months later, the patient developed shingles, treatment with acyclovir was successful. The patient is alive with well-functioning graft 1 year later without evidence for recurrent adenovirus nephritis.

Our patient was exposed to intensified immunosuppression including two courses of rituximab for pre-RT desensitizing and acute humoral rejection, whole plasma exchange and ATG induction. Rituximab causes prolonged hypogammaglobulinemia and may have played an important role in the development of this infection. In one case, rituximab therapy resulted in fulminant adenoviral hepatitis [32]. Adenovirus nephritis may be accompanied by hemorrhagic cystitis [3,9–15,18,33–42]. Data on 10 single patients (five men/five women) including four children with adenovirus nephritis after RT have been published (Table 1) [9–14,43–46]; two patients had combined kidney–pancreas transplantation and in these cases the pancreas allograft was not involved. Onset post-RT ranged between few weeks to several years and only in three cases cystitis or systemic infection was also observed. In all cases, once diagnosis was made, the outcome was favorable. There was no unique therapeutic approach. Some patients responded to reduction in the level of immunosuppression; applied antiviral agents included cidofovir, ribavarin, imunoglobulins, ganciclovir/acyclovir and alpha interferon. Eight of the 11 cases (including the patient covered in this report) were treated during the past 5 years. Two cases of adenoviral nephritis (Table 2) involved immunocompetent individuals and both had good outcome [16,47]; two HIV-infected patients with adenovirus nephritis died from other opportunistic infections [33,48]. Six articles on adenovirus nephritis in SC recipients including three case reports had been published; one series also included chemotherapy patients [3,34,49–53]. One large series comprised only autopsy cases and in the largest published series, the majority of cases were also diagnosed postmortem. Many patients suffered from graft-versus-host disease [3]. The reported outcome in renal recipients is better than that in SC recipients. This may partially reflect earlier diagnosis and treatment in RT patients whose graft status is being monitored by kidney biopsies. In SC recipients and HIV patients, hemorrhagic cystitis and necrotizing tubulointerstitial nephritis commonly develop together. The main goal of therapy is to re-establish immunocompetence; our patient responded well to significant reduction in the TAC dose and discontinuation of MMF without antiviral therapy. Cidofovir has been successfully used but may cause significant nephrotoxicity [54]. Ribavirin and immunoglobulins have also been used [11] and gancichovir (GCV) was found to have a protective effect [49]. To summarize, adenoviral nephritis may develop after intensified immunosuppression. Granulomas on biopsy are highly suggestive, final diagnosis is made by immunohistochemistry. Reduction of immunosuppression may reverse the condition without need for toxic antiviral therapy.

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References

1. Lenaerts L, De Clercq E, Naesens L. Clinical features and treatment of adenovirus infections. *Rev Med Virol* 2008; **18161**: 357.
2. Rocholl C, Gerber K, Daly J, Pavia AT, Byington CL. Adenoviral infections in children: the impact of rapid diagnosis. *Pediatrics* 2004; **113**: e51.
3. Bruno B, Zager RA, Boeckh MJ, *et al.* Adenovirus nephritis in hematopoietic stem-cell transplantation. *Transplantation* 2004; **77**: 1049.
4. Adeyi OA, Randhawa PA, Nalesnik MA, *et al.* Posttransplant adenoviral enteropathy in patients with small bowel transplantation. *Arch Pathol Lab Med* 2008; **132**: 703.
5. Ison MG. Adenovirus infections in transplant recipients. *Clin Infect Dis* 2006; **43**: 331.
6. van Tol MJ, Kroes AC, Schinkel J, *et al.* Adenovirus infection in paediatric stem cell transplant recipients: increased risk in young children with a delayed immune recovery. *Bone Marrow Transplant* 2005; **36**: 39.
7. Perez D, McCormack L, Petrowsky H, Jochum W, Mullhaupt B, Clavien PA. Successful outcome of severe adenovirus hepatitis of the allograft following liver transplantation. *Transpl Infect Dis* 2007; **9**: 318.
8. Hierholzer JC. Adenoviruses in the immunocompromised host. *Clin Microbiol Rev* 1992; **5**: 262.
9. Alsaad KO, Tobar A, Belanger E, Ahmad M, Cattran DC, Herzenberg AM. Late-onset acute haemorrhagic necrotizing granulomatous adenovirus tubulointerstitial nephritis in a renal allograft. *Nephrol Dial Transplant* 2007; **22**: 1257.
10. Asim M, Chong-Lopez A, Nickeleit V. Adenovirus infection of a renal allograft. *Am J Kidney Dis* 2003; **41**: 696.
11. Emovon OE, Lin A, Howell DN, *et al.* Refractory adenovirus infection after simultaneous kidney-pancreas transplantation: successful treatment with intravenous ribavirin and pooled human intravenous immunoglobulin. *Nephrol Dial Transplant* 2003; **18**: 2436.
12. Keswani M, Moudgil A. Adenovirus-associated hemorrhagic cystitis in a pediatric renal transplant recipient. *Pediatr Transplant* 2007; **11**: 568.
13. Kim SS, Hicks J, Goldstein SL. Adenovirus pyelonephritis in a pediatric renal transplant patient. *Pediatr Nephrol* 2003; **18**: 457.
14. Lim AK, Parsons S, Ierino F. Adenovirus tubulointerstitial nephritis presenting as a renal allograft space occupying lesion. *Am J Transplant* 2005; **5**: 2062.
15. Longerich T, Haferkamp K, Tox U, Schirmacher P. Acute liver failure in a renal transplant patient caused by adenoviral hepatitis superimposed on a fibrosing cholestatic hepatitis B. *Hum Pathol* 2004; **35**: 894.
16. Matsukura H, Kida K, Miya K, Kanegane H, Arai M, Miyawaki T. Gross hematuria as a manifestation of membranous nephropathy. *Clin Nephrol* 2007; **68**: 339.
17. Shindo K, Kitayama T, Ura T, *et al.* Acute hemorrhagic cystitis caused by adenovirus type 11 after renal transplantation. *Urol Int* 1986; **41**: 152.
18. Hatakeyama N, Suzuki N, Kudoh T, Hori T, Mizue N, Tsutsumi H. Successful cidofovir treatment of adenovirus-associated hemorrhagic cystitis and renal dysfunction after allogenic bone marrow transplant. *Pediatr Infect Dis J* 2003; **22**: 928.
19. Araya CE, Gonzalez-Peralta RP, Skoda-Smith S, Dharnidharka VR. Systemic Epstein–Barr virus infection associated with membranous nephropathy in children. *Clin Nephrol* 2006; **65**: 160.
20. Cathro HP, Schmitt TM. Cytomegalovirus glomerulitis in a renal allograft. *Am J Kidney Dis* 2008; **52**: 188.
21. Dall A, Hariharan S. BK virus nephritis after renal transplantation. *Clin J Am Soc Nephrol* 2008; **3**(Suppl. 2): S68.
22. Ferluga D, Vizjak A. Hantavirus nephropathy. *J Am Soc Nephrol* 2008; **19**: 1653.
23. Silbert PL, Matz LR, Christiansen K, Saker BM, Richardson M. Herpes simplex virus interstitial nephritis in a renal allograft. *Clin Nephrol* 1990; **33**: 264.
24. Bayrakci US, Baskin E, Sakalli H, Karakayali H, Haberal M. Rituximab for post-transplant recurrences of FSGS. *Pediatr Transplant* 2008. Epub ahead of print.
25. Lee JJ, Lam MS, Rosenberg A. Role of chemotherapy and rituximab for treatment of posttransplant lymphoproliferative disorder in solid organ transplantation. *Ann Pharmacother* 2007; **41**: 1648.
26. Venetz JP, Pascual M. New treatments for acute humoral rejection of kidney allografts. *Expert Opin Investig Drugs* 2007; **16**: 625.
27. Cheson BD, Leonard JP. Monoclonal antibody therapy for B-cell non-Hodgkin's lymphoma. *N Engl J Med* 2008; **359**: 613.
28. Looney RJ, Anolik JH, Campbell D, *et al.* B cell depletion as a novel treatment for systemic lupus erythematosus: a phase I/II dose-escalation trial of rituximab. *Arthritis Rheum* 2004; **50**: 2580.
29. Vo AA, Lukovsky M, Toyoda M, *et al.* Rituximab and intravenous immune globulin for desensitization during renal transplantation. *N Engl J Med* 2008; **359**: 242.
30. Lee MY, Chiou TJ, Hsiao LT, *et al.* Rituximab therapy increased post-transplant cytomegalovirus complications in

Non-Hodgkin's lymphoma patients receiving autologous hematopoietic stem cell transplantation. *Ann Hematol* 2008; **87**: 285.
31. Ferrari A, Luppi M, Marasca R, *et al.* BK virus infection and neurologic dysfunctions in a patient with lymphoma treated with chemotherapy and rituximab. *Eur J Haematol* 2008; **81**: 244.
32. Iyer A, Mathur R, Deepak BV, Sinard J. Fatal adenoviral hepatitis after rituximab therapy. *Arch Pathol Lab Med* 2006; **130**: 1557.
33. Mazoyer E, Daugas E, Verine J, *et al.* A case report of adenovirus-related acute interstitial nephritis in a patient with AIDS. *Am J Kidney Dis* 2008; **51**: 121.
34. Mori K, Yoshihara T, Nishimura Y, *et al.* Acute renal failure due to adenovirus-associated obstructive uropathy and necrotizing tubulointerstitial nephritis in a bone marrow transplant recipient. *Bone Marrow Transplant* 2003; **31**: 1173.
35. Gavin PJ, Katz BZ. Intravenous ribavirin treatment for severe adenovirus disease in immunocompromised children. *Pediatrics* 2002; **110**: e9.
36. Hale GA, Heslop HE, Krance RA, *et al.* Adenovirus infection after pediatric bone marrow transplantation. *Bone Marrow Transplant* 1999; **23**: 277.
37. Hoffman JA. Adenoviral disease in pediatric solid organ transplant recipients. *Pediatr Transplant* 2006; **10**: 17.
38. Hoffman JA, Shah AJ, Ross LA, Kapoor N. Adenoviral infections and a prospective trial of cidofovir in pediatric hematopoietic stem cell transplantation. *Biol Blood Marrow Transplant* 2001; **7**: 388.
39. Humar A, Kumar D, Mazzulli T, *et al.* A surveillance study of adenovirus infection in adult solid organ transplant recipients. *Am J Transplant* 2005; **5**: 2555.
40. Kojaoghlanian T, Flomenberg P, Horwitz MS. The impact of adenovirus infection on the immunocompromised host. *Rev Med Virol* 2003; **13**: 155.
41. Legrand F, Berrebi D, Houhou N, *et al.* Early diagnosis of adenovirus infection and treatment with cidofovir after bone marrow transplantation in children. *Bone Marrow Transplant* 2001; **27**: 621.
42. Pham TT, Burchette JL Jr, Hale LP. Fatal disseminated adenovirus infections in immunocompromised patients. *Am J Clin Pathol* 2003; **120**: 575.
43. Friedrichs N, Eis-Hubinger AM, Heim A, Platen E, Zhou H, Buettner R. Acute adenoviral infection of a graft by serotype 35 following renal transplantation. *Pathol Res Pract* 2003; **199**: 565.
44. Mathur SC, Squiers EC, Tatum AH, *et al.* Adenovirus infection of the renal allograft with sparing of pancreas graft function in the recipient of a combined kidney-pancreas transplant. *Transplantation* 1998; **65**: 138.
45. Shinohara Y, Hashimoto K, Ikegami M, *et al.* Hemorrhagic kidney graft pyelonephritis caused by type 37 adenovirus infection. *Transplant Proc* 1992; **24**: 1565.
46. Tomoe H, Onitsuka S, Nishino S, *et al.* Adenovirus-induced kidney graft pyelonephritis following renal transplantation. *Hinyokika Kiyo* 1994; **40**: 1005.
47. Erdogan O, Bulbul M, Demircin G, Oner A, Memis L. Acute necrotizing tubulointerstitial nephritis due to systemic adenoviral infection. *Pediatr Nephrol* 2001; **16**: 265.
48. Shintaku M, Nasu K, Ito M. Necrotizing tubulo-interstitial nephritis induced by adenovirus in an AIDS patient. *Histopathology* 1993; **23**: 588.
49. Bruno B, Gooley T, Hackman RC, Davis C, Corey L, Boeckh M. Adenovirus infection in hematopoietic stem cell transplantation: effect of ganciclovir and impact on survival. *Biol Blood Marrow Transplant* 2003; **9**: 341.
50. Ito M, Hirabayashi N, Uno Y, Nakayama A, Asai J. Necrotizing tubulointerstitial nephritis associated with adenovirus infection. *Hum Pathol* 1991; **22**: 1225.
51. Iyama S, Matsunaga T, Fujimi A, *et al.* Successful treatment with oral ribavirin of adenovirus-associated hemophagocytic syndrome in a stem cell transplantation recipient. *Rinsho Ketsueki* 2005; **46**: 363.
52. Liles WC, Cushing H, Holt S, Bryan C, Hackman RC. Severe adenoviral nephritis following bone marrow transplantation: successful treatment with intravenous ribavirin. *Bone Marrow Transplant* 1993; **12**: 409.
53. Neofytos D, Ojha A, Mookerjee B, *et al.* Treatment of adenovirus disease in stem cell transplant recipients with cidofovir. *Biol Blood Marrow Transplant* 2007; **13**: 74.
54. Engelmann G, Heim A, Greil J, *et al.* Adenovirus infection and treatment with cidofovir in children after liver transplantation. *Pediatr Transplant* 2008. Epub ahead of print.

