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International Congress of Supportive Care of Patients with Childhood Cancer

Urmia University of Medical Sciences

IRSTH
Iranian Society of Thrombosis and Hemostasis

Report of a known case of recurrent Acute Myeloid Leukemia with BK virus grade IV hemorrhagic cystitis after allogenic transplantation with dramatic response to IV and intravesical cidofovir

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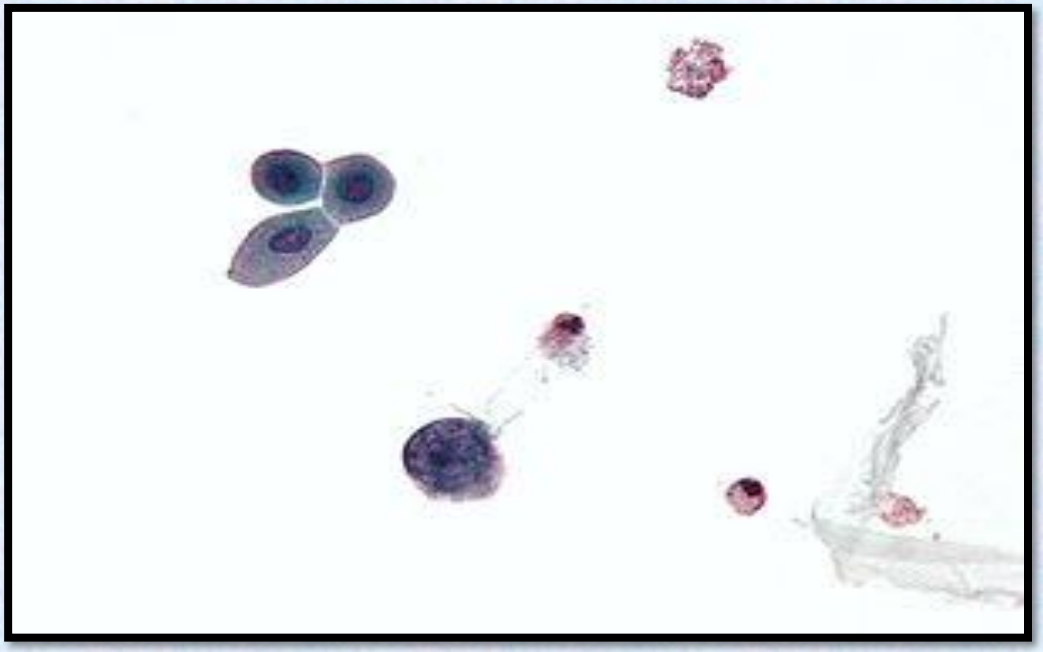
18 - 20 Sep, 2019

BK Virus

The BK virus is a member of the **polyomavirus** family. Past infection with the BK virus is widespread, but significant consequences of infection are uncommon, with the exception of the immunocompromised and the immunosuppressed.

Scientific name: BK virus
Rank: Species
Higher classification: Polyomavirus
Group: Group I (dsDNA)
Family: Polyomaviridae



Urine cytology specimen
Micrograph showing a polyomavirus infected cell

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What is BK virus?

BK virus is an abbreviation of the name of the first patient whom the virus was isolated from in 1971(the patient was then 29 years old).

BK virus is a virus that most people get in **childhood**.

Symptoms can feel like a common **cold**.

Once you get a BK virus infection, the virus stays in your system for good. But it does **not cause** a problem for most people.

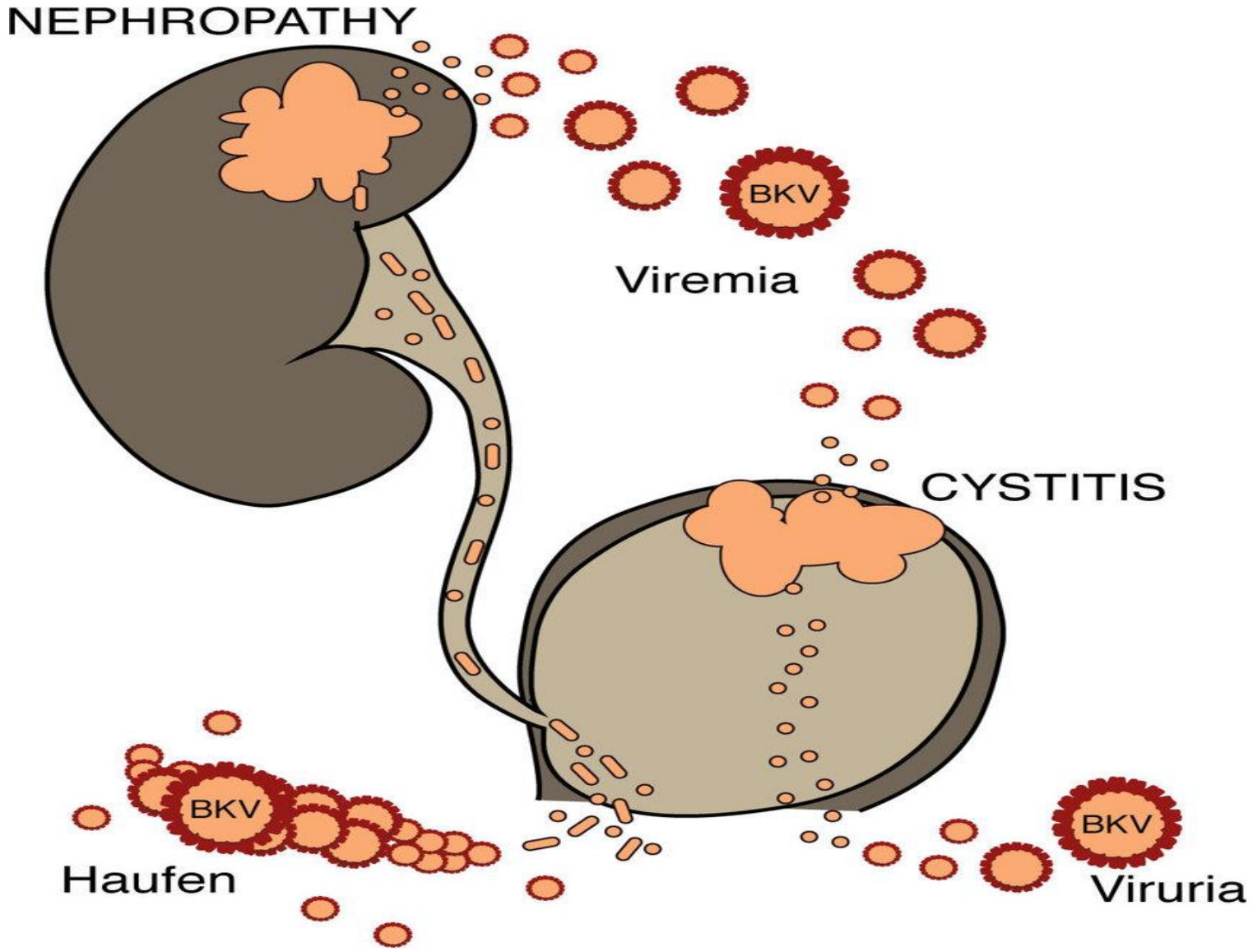
This is **called** latent, or like being '**asleep**' in your body.

Sometimes, when your **immune system** is not working well, the virus wakes up. Then it can cause symptoms of infection.

History

The BK virus was first isolated in 1971 from the urine of a renal transplant patient, initials B.K. The BK virus is similar to another virus called the JC virus (JCV), since their genomes share 75% sequence similarity.

Both of these viruses can be identified and differentiated from each other by carrying out serological tests using specific antibodies or by using a PCR based genotyping approach.


NEPHROPATHY
BKV
Viremia
CYSTITIS
BKV
Haufen
BKV
Viruria

What increases the risk for BK virus infection?

- Organ transplant, like a kidney transplant
- Kidney surgery or injury
- Older age
- Health conditions that weaken your immune system (HIV and Diabetes, to name a few)

- The virus then disseminates to the kidneys and urinary tract where it persists for the life of the individual.
- It is thought that up to 80% of the population contains a latent form of this virus, which remains latent until the body undergoes some form of immunosuppression.
  - Typically, this is in the setting of kidney transplantation or multi-organ transplantation.
  - Presentation in these immunocompromised individuals is much more severe.
  - Clinical manifestations include renal dysfunction (seen by a progressive rise in serum creatinine), and an abnormal urinalysis revealing renal tubular cells and inflammatory cells.

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How will I know if the BK virus is in my system?

Your healthcare provider will check for signs of the virus in your system. They will check both before and after receiving your kidney transplant. Since BK virus can "wake up," it is important to watch for signs of infection.

Symptoms may include:

- Changes in vision, like blurred vision
- Changes in the color of your urine (urine that is brown or red in color)
- Pain when you urinate
- Difficulty urinating
- Needing to urinate more than is normal for you
- A cough, cold, or trouble breathing
- Fever, muscle pain, or weakness
- Seizures

Transmission

It is not known how this virus is transmitted.

It is known, however, that the virus is spread from person to person, and not from an animal source.

It has been suggested that this virus may be transmitted through respiratory fluids or urine, since infected individuals periodically excrete virus in the urine.

A survey of 400 healthy blood donors was reported as showing that 82% were positive for IgG against BK virus.

Detection by Real Time PCR

Real time PCR is the method of choice for routine BK virus screening in organ transplant recipients.

It is several times more sensitive than urine cytology, and can distinguish BK virus from polyomavirus JC.

Treatment

The cornerstone of therapy is reduction in immunosuppression. A recent surge in BK virus associated nephropathy (BKVAN) correlates with use of potent immunosuppressant drugs, such as tacrolimus and mycophenolate mofetil (MMF).

Most common methods:

1. Withdrawal of MMF or tacrolimus
2. Replacement of tacrolimus by cyclosporine
3. Overall reduction of immunosuppressive load
4. Some cyclosporine trough levels reported to be reduced to 100–150 ng/ml and tacrolimus levels reduced to 3–5 ng/ml

Other therapeutic options include **Leflunomide**, **Cidofovir**, **IVIG**, and the **fluoroquinolones**.

Other treatment options

Quinolone antibiotics: Ciprofloxacin (Cipro) was shown to significantly lower viral loads but no data on survival and graft loss exist.

Intravenous immunoglobulin (IVIG) has use in the treatment of infection and allograft rejection – hard to distinguish [clarification needed].

Cidofovir has limited data and is highly nephrotoxic.

Leflunomide in BKVAN

Leflunomide, a pyrimidine synthesis inhibitor is now generally accepted as the second treatment option behind reduction of immunosuppression.

The rationale behind using leflunomide in BKVAN comes from its combined immunosuppressive and antiviral properties.

There are no dosing guidelines for leflunomide in BKVAN. Patient to patient variability has made dosing and monitoring of leflunomide extremely difficult.

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Report of a known case of recurrent Acute Myeloid Leukemia with BK virus grade IV hemorrhagic cystitis after allogenic transplantation with dramatic response to IV and intravesical cidofovir

Gender: male

Weight: 86 / Height: 160 / BMI: 33/5

Date of birth: 1385/10/17

Date of symptoms: 1396/02/15

Date of diagnosis: 1396/02/20

Age of diagnosis: 10 years and 4 months

Diagnosis: Leukemia-AML-M4

Date of therapy: 1396/02/23

Treatment methods used:

1) Date of Chemotherapy: 96/02/23

AML-BFM98 protocol

2) Date of Radiotherapy: 96/07/23-96/07/30 (12G, CNS local)

Event: 1 Relapse (97/04/13)

FLAG protocol

3) Date of BMT: 97/06/12 allogenic from brother

Graft-versus-host disease (GvHD):

97/07/10 - Isolation of **BK Virus**

Family history:

Father: Thalassemia minor

Mother: Familial Mediterranean fever (FMF) / Abortion history

Underlying disease:

Non-Alcoholic Fatty Liver Disease (NAFLD)-GII

High Triglyceride Levels

Now

This is a good general

Not AML, GVHD and BK virus

(NAFLD)-GII

High Triglyceride Levels

Patient:	[redacted]	**Software :**	Partec Report
		Cytometer :	Cyflow Space
Age:	10Y	**Data File :**	abbaszadeh soremi-A1708-bm-33.FCS
Sex:	Male		
Sample ID :	2208		
Physician:	Dr.MEHRVAR	**Date Acquired :**	96/02/19
Director:	Dr.FALLAH AZAD	**Date Analysed :**	96/02/20
Operator:	HAGHIGHI	**No. Flow :**	A96-02-1708

FLOW CYTOMETRIC IMMUNOPHENOTYPING ANALYSIS

SPECIMEN:BM
VIABILITY:90%
GATE:Blast(80%)

HLA-DP, DQ,DR	38.8	CD 20	3.6	CD 235a	2.3
CD 1a	-	CD 22	-	CD 38	70.1
CD 2	10.9	CD 23	-	TdT	0.3
CD 3	9.9	CD 25	-	FMC7	-
CD 4	27.5	CD 33	64.0	IgM	2.4
CD 5	9.9	CD 34	1.5	Mpo	35.4
CD 7	10.0	CD 41	2.5	CD4/CD8(dual)	-
CD 8	10.5	CD 45	-	CD2/CD19(dual)	0.2
CD 10	0.4	CD 61	1.3	CD3/HLADR(dual)	1.4
CD 11	-	CD 64	51.3	CD5/ CD20(dual)	-
CD 13	24.0	CD 71	6.5	CD5/ CD19(dual)	-
CD 14	4.9	CD 79a	-	CD10/ CD19(dual)	-
CD 15	40.0	CD 103	-		
CD 19	3.8	CD 117	33.4		

Diagnosis :BM immunophenotyping is consistent with AML,more compatible with AML-M4.

V. FALLAH AZAD
MD.APCP

دکتر وحید فلاح آزاد
پزشک متخصص آسیب شناسی بالینی و تشریحی
ن . پ ۶۵۳۹۴ ن . آ ۱۹۰۴
بیمارستان فوق تخصصی محک

Patient: [redacted]
Age:
Sex: Male
Sample ID : 1588
Physician: Dr.MEHRVAR
Director: Dr.FALLAH AZAD
Operator: HAGHIGHI

Software : Partec Report
Cytometer : Cyflow Space
Data File : abbaszadeh soremi-A3791-bm-117.FCS
Date Acquired : 97/04/13
Date Analysed : 97/04/14
No. Flow : A97-04-3791

FLOW CYTOMETRIC IMMUNOPHENOTYPING ANALYSIS

SPECIMEN:BM
VIABILITY:90%
GATE:Suspicious cells(20%)

HLA-DP, DQ,DR	41.7	CD 20	3.6	CD 235a	-
CD 1a	-	CD 22	-	CD 38	-
CD 2	9.4	CD 23	-	TdT	-
CD 3	11.9	CD 25	-	FMC7	-
CD 4	13.7	CD 33	75.7	IgM	-
CD 5	14.0	CD 34	4.8	Mpo	-
CD 7	8.2	CD 41	-	CD4/CD8(dual)	0.6
CD 8	4.2	CD 45	-	CD2/CD19(dual)	0.4
CD 10	4.7	CD 61	-	CD3/HLADR(dual)	4.3
CD 11	-	CD 64	52.2	CD5/ CD20(dual)	-
CD 13	54.6	CD 71	-	CD5/ CD19(dual)	-
CD 14	6.0	CD 79a	-	CD10/ CD19(dual)	-
CD 15	23.1	CD 103	-		
CD 19	2.9	CD 117	79.5		

Diagnosis :BM immunophenotyping is consistent with AML-M4,Relapse.

V. FALLAH AZAD
MD.APCP

دکتر وحید فلاح آزاد
ورد تخصصی آسیب شناسی بالینی و تشریحی
ن ۰۰ ۶۵۳۹۲
بیمارستان فوق تخصصی محک
ن ۰ آ ۱۹۰۴

Protocol of Allogeneic BLOOD and Marrow Transplantation in AML and MDS

Patient name: [redacted] Age: 12 Ht: 164cm Wt: 113kg BSA: 2.14

For obese patients: > 14Y AIBW <14Y IBW (50th percentile) **AIBW=58.25**

Patient BGRh: **A+** Donor name and BGRh: **A+ (brother)**

Karnofsky performance score: (acceptable >60)

S		Conditioning	U	CS.A	Leu	B.	Zo	ZY
-7	(97/6/8)	Busulfan = 90mg/Q6h				X	X	X
-6	(97/6/8)	Busulfan = 90mg/Q6h				X	X	X
-5	(97/6/8)	Busulfan = 90mg/Q6h				X	X	X
-4	(97/6/8)	Busulfan = 90mg/Q6h				X	X	X
-3	(97/6/9)	Endoxan(cyclophosphamide = 3500mg	X			X	X	X
-2	(97/6/10)	Endoxan(cyclophosphamide = 3500mg	X			X	X	X
-1**	(97/6/11)	melphalan = 300 mg	X	X			X	X
0	(97/6/12)	HST		X				
+1		MTX (24h after SCT) = 10mg		X			X	
+2				X	X		X	
+3		MTX = 10 mg		X			X	
+4				X	X		X	
+5				X			X	
+6		MTX = 10 mg		X			X	

Refrences:

- Guidelines for Hematopoietic stem cell Transplantation (HSCT) IN Childhood MDS and JMML for patients enrolled in EWOG-MDS Consensus Conference Freiburg, October 25/26, 2016 _ Version 1.3, 15.08.2017.

Discussion on strategy for GvHD prophylaxis and treatment:

HLA-identical Sibling BM/PBSC donor and patient at **HSCT < 12** years CSA 1.5 mg/kg in 2-hour infusion twice a day (total dose 3 mg/kg/day) starting from day -1 and with the objective of maintaining serum levels between 100-200 ng/ml (continuous infusion over 24 hours is also acceptable) ; **HLA-identical Sibling BM/PBSC donor and patient at HSCT ≥ 12 years CSA 1.5 mg/kg in 2-hour infusion** twice a day (total dose 3 mg/kg/day) and short course MTX (3 doses on days +1 , +3 and +6 at a dosage of 10 mg/m^2).

Not detect (Urine=U & Plasma=P)	BKv (Urine)	date
JCV(U,P)/SV40(U,P)/CMV(U,P)/Adenomav(U,P)/BKv(P)	7.128.037.228 IU/ML	97/07/10
HSVI(U,P)/HSVII(U,P)/JCV(U,P)/SV40(U,P)/CMV(U,P)/BKv(P)	211.335.019.480 IU/ML	97/07/16
JCV(U,P)	14.838.461 IU/ML	97/07/18
HSVI(U,P)/HSVII(U,P)/JCV(U,P)/SV40(U,P)/ CMV(U,P)/BKv(P)	3.063.636 IU/ML	97/07/21
CMV(U,P)/JCV(U,P)/BKv(P)	5.192.176 IU/ML	97/07/25
CMV(U,P)/JCV(U,P)/BKv(P)	511.818 IU/ML	97/07/28
CMV(U,P)/JCV(U,P)/BKv(P)	3.200.000 IU/ML	97/08/01
	3.368.685 IU/ML	97/08/03
SV40(P)/JCV(P)/BKv(P)	3.006.090 IU/ML	97/08/06
JCV(U)	1.305.000 IU/ML	97/08/09
	1.969 IU/ML	97/08/21

Quantitative Real Time PCR Report

File No:97074473

Name of the Patient : [redacted]

Gender/Age: Male/12

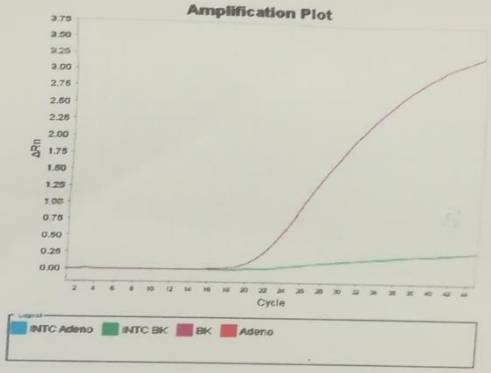
Type of Sample: Urine

Test Name: BKV

Method: Taqman Hot Start Q-PCR

Protocol: Using Gene proof IVD kit.

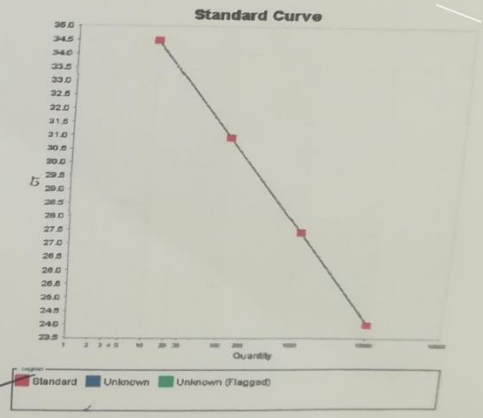
Instrument Name:ABI Step One plus Real Time PCR *



Result : BKV DNA detected load 7128037228 IU/ml.

(9.85 log)

In this assay 1 IU/ml = 1 Copies/ml



غـزل ذوالفقـار
کارشناس آزمایشگاه
بیـمارسـتان نیـکان

* Applied Biosystems Technology for Real Time PCR Receives Best New Product Award - Select Science Magazine

Hemorrhagic Cyctitis: Grade IV

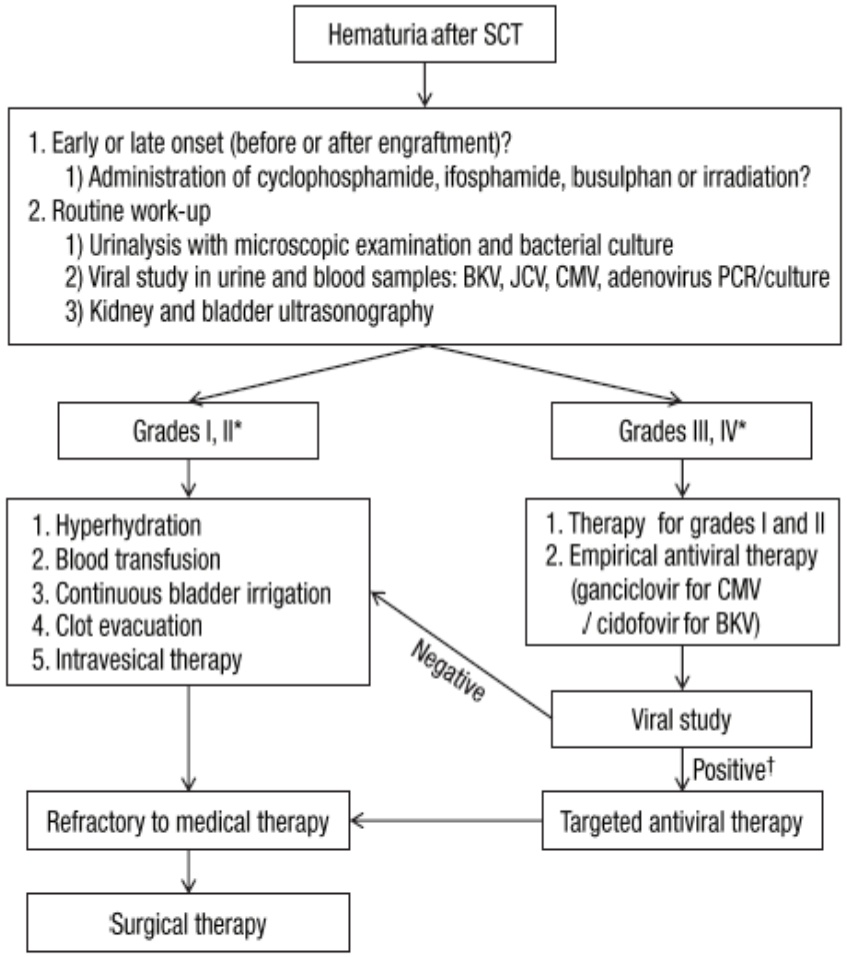


Fig. 1. Diagnostic and therapeutic algorithm for stem cell transplant recipients with hemorrhagic cystitis. SCT, stem cell transplantation; BKV, BK virus; JCV, JC virus; CMV, cytomegalovirus; PCR, polymerase chain reaction. *See Table 1. †For BKV: urinary BKV DNA titer>10^7 copies/mL and serum BKV DNA titer>10^4 copies/mL.

Review article
Korean J Pediatr 2014;57(12):514-519
http://dx.doi.org/10.3345/kjp.2014.57.12.514
pISSN 1738-1061•eISSN 2092-7258

Korean J Pediatr

BK virus-associated hemorrhagic cystitis after pediatric stem cell transplantation

Seung Beom Han, MD[1,2], Bin Cho, MD, PhD[1,3], Jin Han Kang, MD, PhD[1,2]
[1]Department of Pediatrics, [2]The Vaccine Bio Research Institute, [3]The Catholic Blood and Marrow Transplantation Center, The Catholic University of Korea College of Medicine, Seoul, Korea

Table 1. Grades of hemorrhagic cystitis

Grade	Manifestations
I	Microscopic hematuria
II	Macroscopic hematuria
III	Macroscopic hematuria with blood clots
IV	Renal impairment due to urinary tract obstruction

four grades based on the severity of hematuria and its effect on the upper urinary tract (Table 1)[14].

Blood products

+1HSCT → **+86HSCT**

irradiated Single-Donor Apheresis platelets: 71times
Irradiated Pc-RBCs : 35 times
Plasma FFP: 14 times

CAP-Valacyclovir
Tab-Tacrolimus

Bkvirus Load

7128037228

CAP-Valacyclovir
Amp-Cidofovir(IV)
Hemodialysisx4

14838461

CAP-Cellcept
Amp-Cidofovir(Intravasical)

511818
3200000
1305000
1969

97/07/10 97/07/18 97/07/28 97/08/01 97/08/09 97/08/21

+29HSCT

IVIG=145gr/IV

97/7/18:

1)Amp Cidofovir (IV): 0/68 mg/kg=75mg

97/8/3:

2)Amp Cidofovir (Intravesical): 0/27 mg/kg=30mg

97/8/9:

3)Amp Cidofovir (Intravesical): 0/68 mg/kg=75mg

97/8/23:

4)Amp Cidofovir (Intravesical): 0/68 mg/kg=75mg

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آزمایش
LAK
LABORATORY
PCR، ژنتیک، تشخیص طبی، هورمون

Molecular Diagnostic Department
PCR Report

ISO 9001 OHSAS 18001 OHSAS 14001
gholhak.lab@gmail.com

PCR No 2960713 **Lab Number** 08-15445 **Date** 1397/08/21

Name : [redacted] **Family :** [redacted]

Sex : Male **Age :** 12 **Physician :** **Dr.** Masoodi

Sample: **Urine**

Test : **BK Quantitative PCR(Urine)** **Result:** **1,969 Copy/ml**

Intnded Use :
To detect BK virus acute infection or reactivation

Materials :
Artus BK Virus RG PCR kit, QIAamp DNA extraction kit

Instrument :
Rotor Gene Q

Methodology :
Amplification of target region by Real Time PCR

Sensitivity :
195 Copies/ml

Specifieity :
95%

Dynamic Range :
-

Sector Manager **Lab Director**

Address: No.1, Kadouyi Ave. , Shariati street, Tehran, Iran **Tel: 0098-21-22600413**

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The general condition of the patient is very good.

Does not take any medication.

Tests	Normal range	Result
W.B.C	4.8-10.8	5.6
R.B.C	4.6-6.2	5.73
H.b	14-17.5	12
H.C.T	41.5-50.4	36.6
M.C.V	80-96	63.87
M.C.H	27-33	20.94
M.C.H.C	32-36	32.79
R.D.W	11-14.5	19.4
PLT	130-400	192
Ferritin	28-365	**1806***
Urea	15-50	35
Creatinine	0.7-1.4 (Male)	1
SGOT (AST)	Up to 37	29
SGPT (ALT	Up to 41	54
I.N.R	1-1.3	1.02
E.S.R 1st hr	0-15	21
CRP (Qualitative)	<6	<6
Bilirubin Direct	<0.25	<0.2
Bilirubin Total	0.1-1.2	0.9

No blast were seen

Acknowledgment

I should thanks from my colleagues in different part of hospital

- Clinical team of treatment
- Laboratory team
- Research team