POLYOMAVİRUS ENFEKSİYONLARI

Yrd. Doç. Dr. Selçuk NAZİK

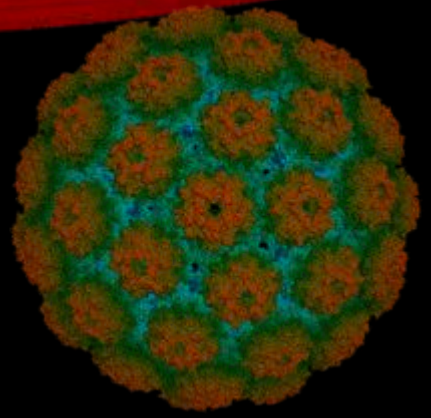
KSÜ TIP FAKÜLTESİ SAĞLIK UYGULAMA MERKEZİ

ENFEKSİYON HASTALIKLARI VE KLİNİK MİKROBİYOLOJİ AD

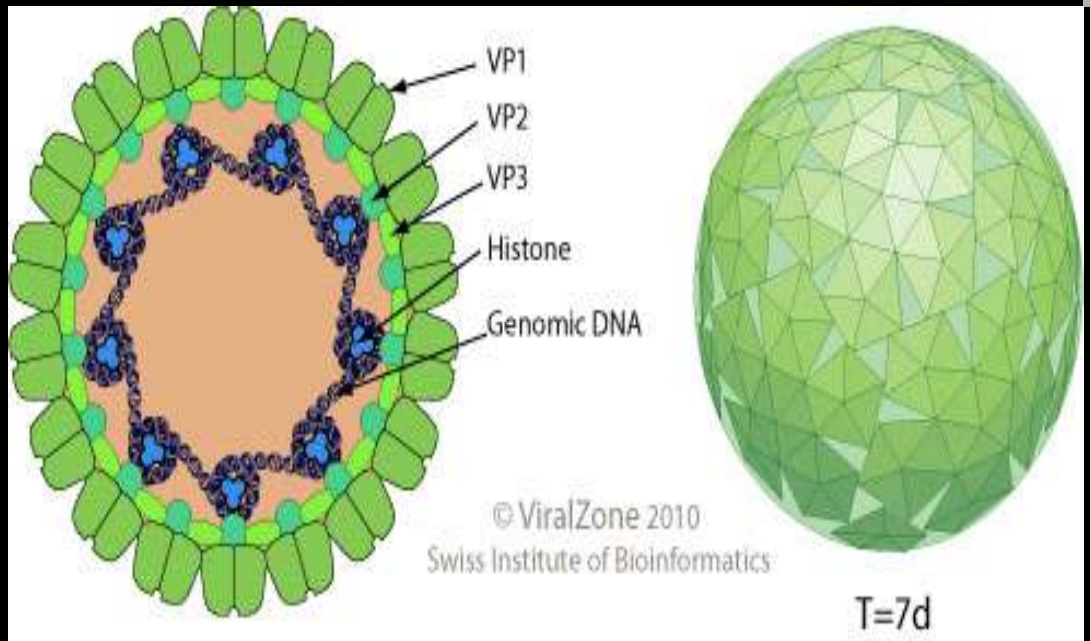
2018 HATAY

SUNUM PLANI

- Virusun tanımlanması ve tarihçesi
- Virusun sınıflaması
- BK virus
- JC virus



- 45 nm
- Zarfsız
- Sirküler çift sarmal DNA



VİROLOJİ

- *Polyomaviridae* ailesi
- Virüslerin çoklu (poly) tümörler (-oma) üretme kabiliyetini ifade eder
- Primer kaynak kuşlar ve memeliler
- 13/77 tür insanı enfekte eder

Species	Proposed genus	Virus name				Clinical correlate (if any)
Human polyomavirus 5	Alpha	Merkel cell polyomavirus				Merkel cell cancer[13]
Human polyomavirus 8	Alpha	Trichodysplasia spinulosa polyomavirus				Trichodysplasia spinulosa[13]
Human polyomavirus 9	Alpha	Human polyomavirus 9				None known
Human polyomavirus 12	Alpha	Human polyomavirus 12				None known
Human polyomavirus 13	Alpha	New Jersey polyomavirus				None known
Human polyomavirus 1	Beta	BK polyomavirus	BKPyV	NC_001538	1971	Polyomavirus-associated nephropathy; haemorrhagic cystitis[13]
Human polyomavirus 2	Beta	JC polyomavirus	JCPyV	NC_001699	1971	Progressive multifocal leukoencephalopathy[13]
Human polyomavirus 3	Beta	KI polyomavirus	KIPyV	NC_009238	2007	None known
Human polyomavirus 4	Beta	WU polyomavirus	WUPyV	NC_009539	2007	None known
Human polyomavirus 6	Delta	Human polyomavirus 6	HPyV6	NC_014406	2010	HPyV6 associated pruritic and dyskeratotic dermatosis (H6PD)[53]
Human polyomavirus 7	Delta	Human polyomavirus 7	HPyV7	NC_014407	2010	HPyV7-related epithelial hyperplasia[53][54][55]
Human polyomavirus 10	Delta	MW polyomavirus	MWPyV	NC_018102	2012	None known
Human polyomavirus 11	Delta	STL polyomavirus	STLPyV	NC_020106	2013	None known

Karolinska Institute

Washington University

Malawi

st Luis

- Tür spesifik
  - Maymunda simnian virus 40 (SV 40) (1960)
  - İnsanda
    - BKV
    - JCV

BK VİRUS

THE LANCET

Volume 297, Issue 7712, 19 June 1971, Pages 1253-1257

Originally published as Volume 1, Issue 7712

ORIGINAL ARTICLES

NEW HUMAN PAPOVAVIRUS (B.K.) ISOLATED FROM URINE AFTER RENAL TRANSPLANTATION

SylviaD. Gardner [a, b], AnneM. Field [a, b], DulcieV. Coleman [b], B. Hulme [b]

JOHN CUNNİNGHAM (JC) VİRUS

THE LANCET

Volume 297, Issue 7712, 19 June 1971, Pages 1257-1260

Originally published as Volume 1, Issue 7712

ORIGINAL ARTICLES

CULTIVATION OF PAPOVA-LIKE VIRUS FROM HUMAN BRAIN WITH PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY

BillieL. Padgett [a, b], GabrieleM. Zurhein [a, b], DuardL. Walker [a, b], RobertJ. Eckroade [a, b], BertH. Dessel [b]

İNSAN POLYOMA VİRÜSLERİ

- Tüm dünyada yaygın
- Dünya genelinde BKV İçin %90, JCV için %86 seropozitiflik
- İmmunkompetanlarda hastalık yapmıyor

RİSKLİ GRUP

- Transplantasyon yapılan hastalar
- Primer veya kazanılmış immün yetmezliği olanlar
- Sitotoksik ilaç/steroid tedavisi alanlar
- DM, Kanser ve Otoimmün hastalığı olanlar

BKV

- 1971 yılında Renal Tx üreteral stenozlu hasta
- 1983 yılında tübülointerstisyel nefrit (6y, E, primer immün yetmezlik)

Gardner SD, et al, Lancet, 1971
Rosen S, et al. NEJM, 1983

BKV

- DNA virüsü
- SV40 ile %70, JCV ile %72 benzerlik gösteriyor
- Subtipleri mevcut I, II, III, IV
  - Subtip I tüm dünyada ve en sık (%80)
  - I/a, I/b1, I/b2 ve I/c
  - Subtip IV özellikle Doğu Asya
  - IV/a1, IV/a2, IV/b1, IV/b2, IV/c1 ve IV/c2

Table 1 BKPyV reference sequences selected for phylogenetic analysis

Subtype/ subgroup	Isolate	Geographic origin	GenBank accession no.
I/a	DUN	USA	NC_001538
I/a	KEN-1	Kenya	AB263926
I/b1	Dik	The Netherlands	AB211369
I/b1	WW	South Africa	AB211371
I/b2	JL	The Netherlands	AB211370
I/b2	FNL-12	Finland	AB263918
I/c	MT	Japan	AB211372
I/c	TW-1	Japan	AB211381
II	ETH-3	Ethiopia	AB263916
II	SB	UK	Z19536
III	AS	UK	M23122
III	KOM-3	Japan	AB211386
IV/a1	VNM-7	Vietnam	AB269869
IV/a1	PHL-8	Philippines	AB269859
IV/a2	MMR-1	Myanmar	AB269841
IV/b1	THK-8	Japan	AB211390
IV/b1	TW-3	Japan	AB211391
IV/b2	KOM-2	Japan	AB211387
IV/b2	JPN-15	Japan	AB269834
IV/c1	MON-1	Mongolia	AB269846
IV/c1	SWC-1	China	AB269863
IV/c2	ITA-4	Italy	AB269833

BKV

- Primer enfeksiyon: subklinik
  - Asemptomatik viral hastalık
- İlk olarak tonsillerde replikasyon
- Lenfoid hücreler ile böbreğe üroepitelyum ve renal tübüler hücrelerde latent
- BKV antikoru yaşla birlikte artar
  - 3 yaşına kadar %50
  - 10 yaşına kadar %60-90
  - 20 yaşına kadar %80-90

BKV REAKTİVASYON

- Böbrek transplant alıcısı
- HSCT alıcısı
- HIV
- SLE
- Wiskott-Aldrich sendromu
- Hiperimmunglobulin M sendromu
- Hodgkin hastalığı
- Nonrenal solid organ transplantı
- Multiple sklerosis
- Natalizumab tedavisi alanlarda

Vallbracht A, et al. Am J Pathol 1993
Sundsfjord A, et al. J Infect Dis 1999
Rosen S, et al. NEJM 1983
de Silva LM, et al. J Med Virol 1995
Egli A, et al. Am J Transplant 2010
Lonergan RM, et al. J Neurovirol 2009

BKV İMMUNOLOJİ

- CD4+ T lenfosit ve IFN ɣ sekresyonu
- T hücreleri, CD8+ Anti –BK yanıtında çok önemli
- BK virus enfeksiyonu (viremi) ile CD8+ sayısı ters orantılı
- Hümoral immünitenin BKV regülasyonu tartışmalı
  - Test standartize değil

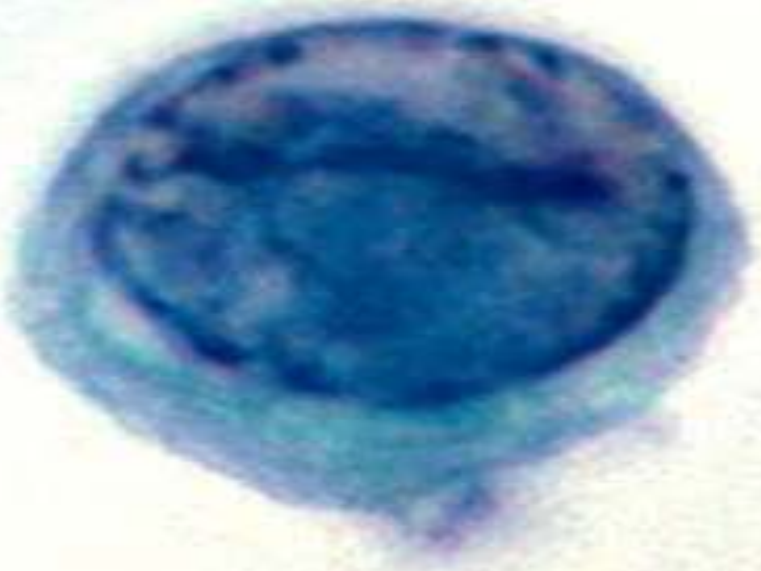
Ginevri F, et al. Am J Transplant 2007
Lamarche C, et al. Transplantation 2016
Comoli P, et al. Transplantation 2004

BKV TANI TESTLERİ

- İdrar
  - Decoy hücreleri
  - DNA-PCR
  - EM-Haufen
  - İdrar sitokinleri : IL3-IL6 (Sadeghi M, etal , 2009)
  - İdrarda mRNA (*Dadhania D, etal. 2013*)
- Kan
  - DNA PCR (kantitatif) PPV ~%60
  - Serum BK PCR >10000 copy/mL ise BK nefropatisi ile ilişkisi %93 spesifisite
- Renal Biyopsi
  - Gold standart

Hirsch HH, et al. 2006

Large cell with high N:C ratio and with smooth glassy appearance of the nucleus.



Polyoma virus (Decoy cells)

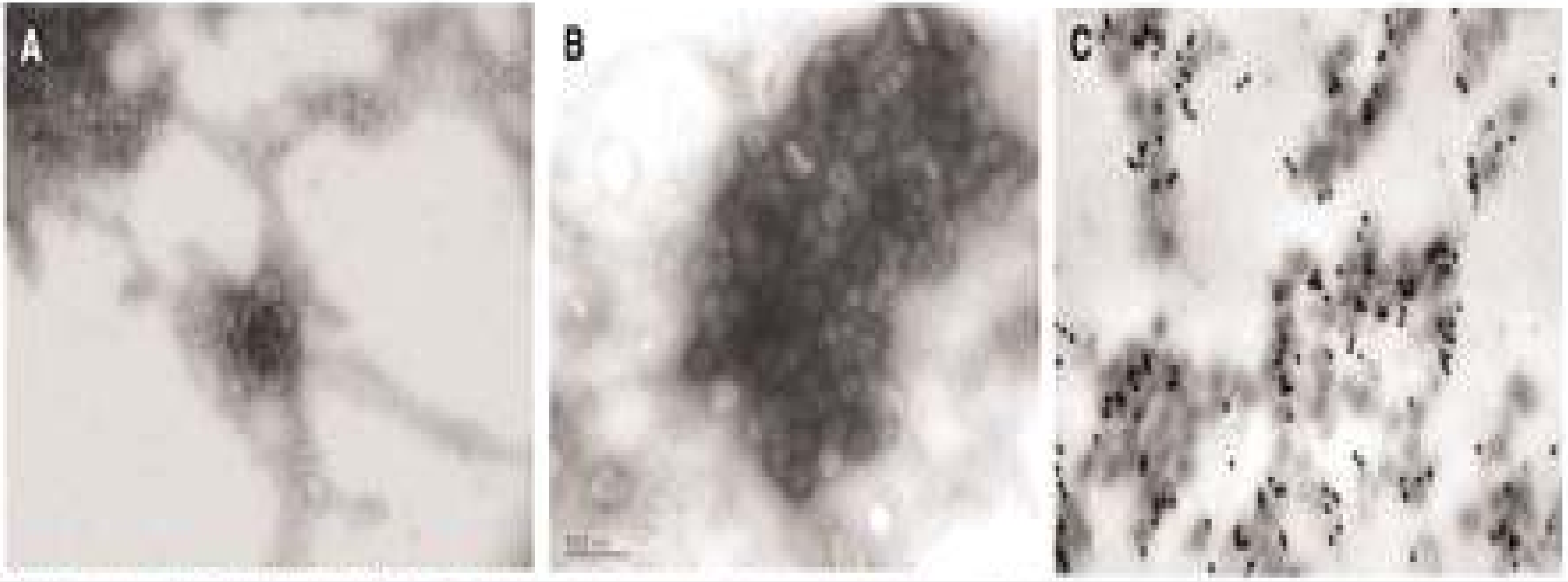


Figure 1.

(A through C) Three-dimensional cast-like polyomavirus aggregates, termed Haufen, in voided urine samples. (A) A small Haufen (nine virions). (B) A large Haufen (>100 virions). (C) Haufen are rich in Tamm-Horsfall protein (marked by the black dots representing gold particles). (A and B, negative staining EM, uranyl acetate counterstaining; C, immunogold labeling EM with a mouse monoclonal anti-human Tamm-Horsfall antibody, 5-nm gold particles). (D and E)

BKV TEDAVİ

- Sidofovir
- Foskarnet
- İnterferon
- Leflunamide
- FK778
- Kinolon

- Spesifik tedavisi YOK
- İmmunsüpresyonu azaltmak
- Adoptif tedavi: BK spesifik T hücre

Archives of Virology
https://doi.org/10.1007/s00705-018-3724-y

ORIGINAL ARTICLE

The prevalence and isolated subtypes of BK polyomavirus reactivation among patients infected with human immunodeficiency virus-1 in southeastern China

Caiqin Hu[1] · Ying Huang[1] · Juwei Su[1] · Mengyan Wang[1] · Qihui Zhou[1] · Biao Zhu[1]

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Abstract

BK polyomavirus (BKPyV) is an opportunistic infectious pathogen that is associated with hemorrhagic cystitis and nephropathy, mainly in transplant recipients and human immunodeficiency virus 1 (HIV-1) infected patients. However, molecular characterization studies of BKPyV in China are rare. This study was designed to elucidate the prevalence and to determine the main subtypes of BKPyV among HIV-1-infected patients in southeastern China. In addition, the increased incidences for BKPyV reactivation were analyzed. The isolated BKPyV DNA was amplified by polymerase chain reaction (PCR) and the specimen sequences were aligned with the reference sequences for phylogenetic analysis. In this study, BKPyV viruria was detected in 64.2% (88/137) of HIV-1-infected patients. Patients in the BKPyV-positive group were more diverse with respect to gender ($P = 0.039$) and age ($P = 0.023$) than their counterparts in the BKPyV-negative group, and they had a higher rate of co-infection with tuberculosis (TB) ($P = 0.026$). Viruria was more commonly found in patients with CD4 counts <200 cells/mm (72.7%) than in those with CD4 counts ≥200 cells/mm (58.5%) (not significant). All sequenced BKPyV isolates belonged to subtype I (13/32) and IV (19/32). A high prevalence of BKPyV reactivation was discovered in patients with HIV-1 infection. Females and elderly individuals, as well as those with a TB co-infection, appeared more susceptible to BKPyV reactivation in this study. BKPyV viruria was found more often and was associated with lower CD4 counts.

Category	Total	No. of BKPyV negatives	No. of BKPyV positives	*P*-value
Overall	137	49 (35.8)	88 (64.2)	
Gender, n (%)				0.039[1]
Male	121	47 (38.8)	74 (61.2)	
Female	16	2 (12.5)	14 (87.5)	
Age, years, n (%)				0.023[2]
≤20	1	1 (100)	0 (0.00)	
21–40	88	34 (38.6)	54 (61.4)	
41–60	35	12 (34.3)	23 (65.7)	
>60	13	2 (15.4)	11 (84.6)	
CD4+ cells/mm, n (%)				0.089[1]
<200	55	15 (27.3)	40 (72.7)	
≥200	82	34 (41.5)	48 (58.5)	
Treatment, n (%)				
Tenofovir	61	21 (34.4)	40 (65.6)	0.769[1]
Zidovudine	43	20 (46.5)	23 (53.5)	0.076[1]
Lamivudine	111	42 (37.8)	69 (62.2)	0.296[1]
Efavirenz	88	35 (39.8)	53 (60.2)	0.190[1]
Comorbidity, n (%)				
Hepatitis B	8	3 (37.5)	5 (62.5)	NS
TB	21	3 (14.3)	18 (85.7)	0.026[1]
Lymphoma	6	2 (33.3)	4 (66.6)	NS
Cryptococcal meningitis	9	5 (55.6)	4 (44.4)	NS
PCP	6	3 (50.0)	3 (50.0)	NS

Case Report

BK Virus Encephalitis in HIV-Infected Pa
Case Report and Review

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Received 1 August 2016; Revised 26 December 2016; Accepted 23 January 2017;

- LP: açılış basıncı 12,5 cm H2O, WBC:3, Protein: 28, Glikoz: 39
- Bakteri, TBC , Cryptococcal antijen ve JC PCR testi: negative
- Tanı: BKV PCR testi BOS'ta (+)
- Diğer organ tutulumu: Yok
- Tedavi: ART
- Sonlanım: Exitus

FIGURE 1: A magnetic resonance image showed a hyperintensity in T2 on the upper and lower right frontal gyri, in the left occipital lobe, and lesions with annular enhancement in the deep upper left temporal sulcus (case report 1).

- 45y, K
- CD4+:23hücre/mm3
- HIV RNA: 167580 copy/mL
- Ateş, baş ağrısı, bulantı, kusma
- MRI:
- LP:, WBC:8, Protein: 133, Glikoz: 40
- Bakteri, TBC , Cryptococcal antijen ve JC PCR testi: negative
- Tanı: BKV PCR testi BOS'ta (+)
- Diğer organ tutulumu: BKV PCR testi idrarda (+), renal biyopsi yok
- Tedavi: ART
- Sonlanım: Sağ

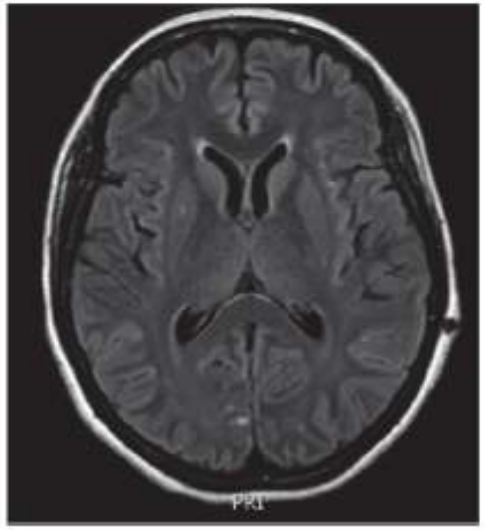
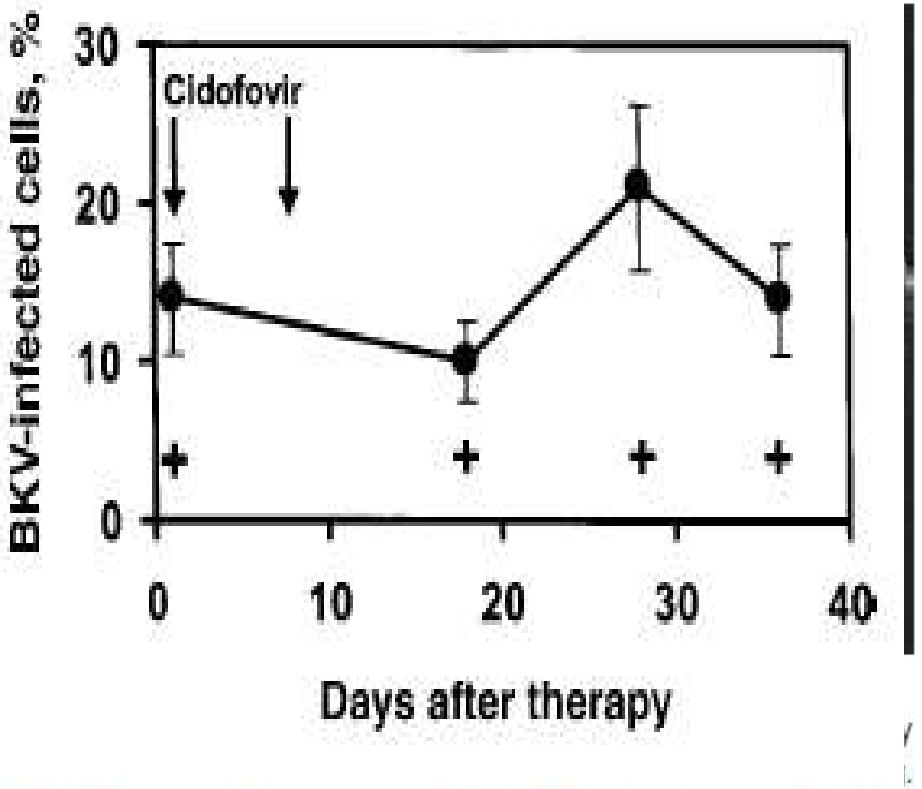
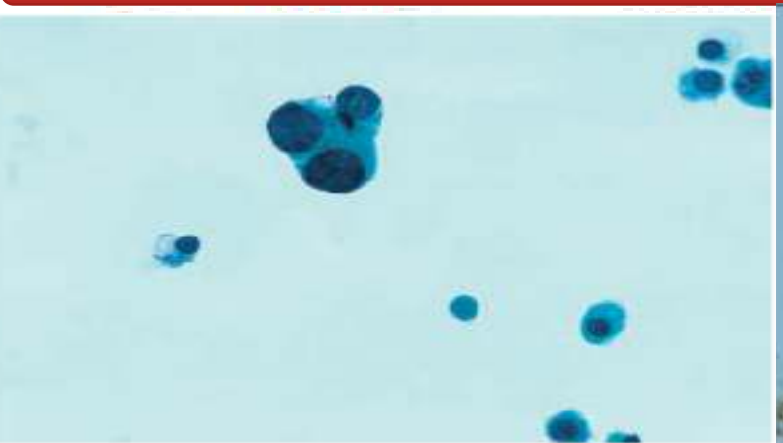


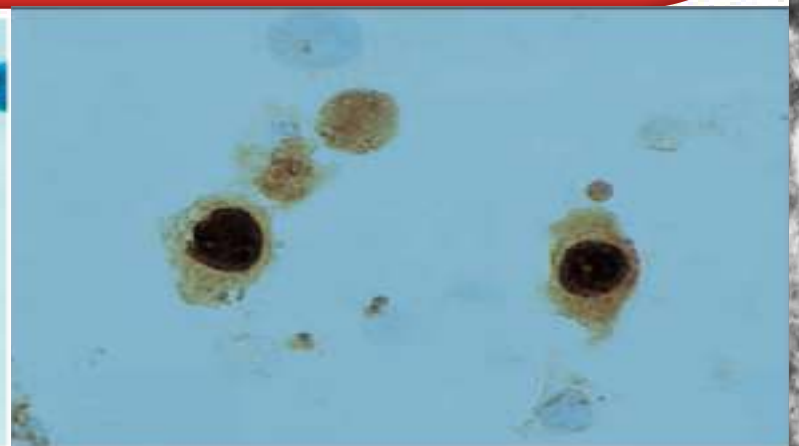
FIGURE 2: Cerebral MRI currently shows mild volume loss with scattered FLAIR hyperintensities and asymmetric lesions without mass effect (case report 2).

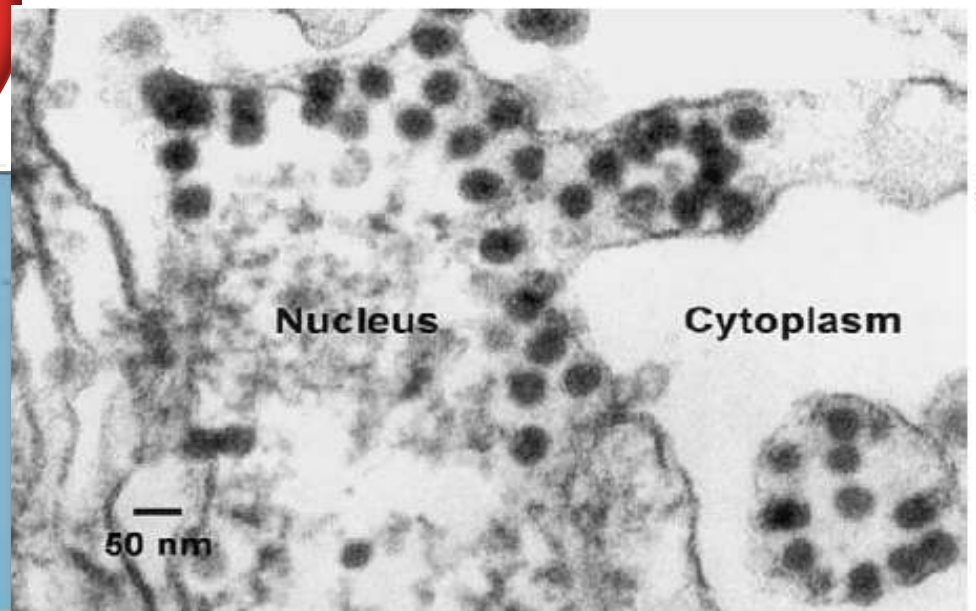
Antoniolli L, et al. Case Report in Medicine, 2017

- 41y, E, HIV
- CD4:780/mL, HIVRNA:134000 copy/mL
- Karın ağrısı…kolonoskopi…çekal kitle Büyük B H'li Lenfoma
- KT:cyclophosphamide, liposomal doxorubicin, vincristine, dexamethasone, and rituximab
- 2 kür CMV antijenemisi ateş
  - Gansiklovir, lamivudine, stavudine ve efavirenz
- HIVRNA:1040 copy/mL
- 3.kür KT sonrası suprapubik gerginlik ve hematüri
- Analjezi, mesane yıkama ve kan Tf….4 hafta
- İdrarda decoy hücresi
- İdrarda BKV PCR (+), JCV PCR (-)
- 2 hafta 5 mg/kg sidofovir infüzyon









JCV

- Çocukluk çağında geçirilir
- Sağlıklı erişkin tonsilde %39 JCV PCR (+)
- Beyin dokusunda latent kalıyor, böbrek, Kİ ve diğer organlar???
- İmmunsüprese olanlarda enfeksiyon oluşur
- Hücresel immün yetmezlik (HIV/AIDS, natalizumab)
- *White MK, Khalili K. J Infect Dis 2011*
- Progresif Multifokal Lökoensefalopati (PML)

PML

- 1958 yılında tanımlanmış KLL + Hodgkin Hastalığı

Astrom KE, et al. Brain 1958

- SSS'nin demiyelinizan hastalığı
- İntrakranial basınç artışı olmadan hızla gelişen ilerleyici fokal nörolojik bozukluklar
- Latent haldeki JCV immünsüpresyon durumunda oligodentrositlerde replike olur
- Litik enfeksiyon sonucu miyelin kılıf harabiyeti meydana getirir

JCV PML

- Farklı boyutlarda demiyelinizan odak (beyaz cevher tutuluyor)
- Tutulum beyin hemisferlerinde > Serebellum ve beyin kökü > Medulla spinalis

- Klinik
  - Mental fonksiyon kaybı, kranial sinir bozuklukları
  - Ataksi
  - Hareket zorluğu
  - Demans
  - Körlük
  - Paralizi
  - Koma ve ölüm

Post MJ, et al. Post MJ 1999

PML RİSK FAKTÖRLERİ

- ART tedavisi öncesinde PML AIDS'li hastaların %5-10'unda …….
- İmmünmodülatör ilaçlar ikinci önemli neden
  - Natalizumab ve Efalizumab
  - Rituximab, belatacept, fingolimod, infliximab, alemtuzumab, mycophenolate mofetil, fludarabine, leflunomide ve fumaric asid esterleri
- Hematolojik veyaa lenforetiküler malignensi
- Otoimmun romatoljik hastalıklar (%0,95)
- Solid organ transplantı (%2,8)
- %6 risk faktörü yok

Bozic C, et al. Eur J Neurol. 2014

Zaheer F, Berger JR Ther Adv Drug Saf. 2012

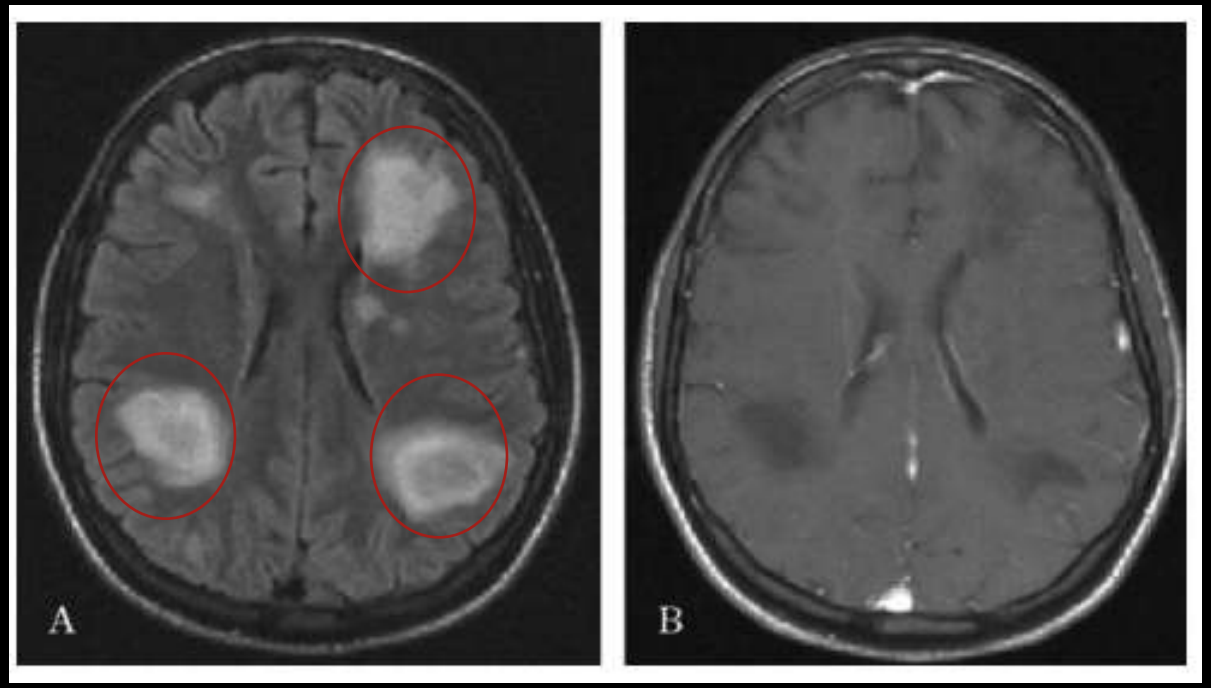
Williamson EM, Berger JR. CNS Drugs. 2015

Bart RE. Curr. Opin Neurol 2006

JCV PML TANI

- Klinik

- Radyolojik
  - Çok sayıda bilateral, asimetrik
  - Kontrast tutmayan demiyelinizan lezyonlar
  - Kitle etkisi yok
  - Hemoraji yok
  - Natalizumab ilişkili PML ve PML IRIS'te kontrast tutulumu
- Virolojik
  - BOS'ta PCR ile JCV-DNA'sının gösterilmesi
    - ART alanlarda %60, almayanlarda %90 oranında

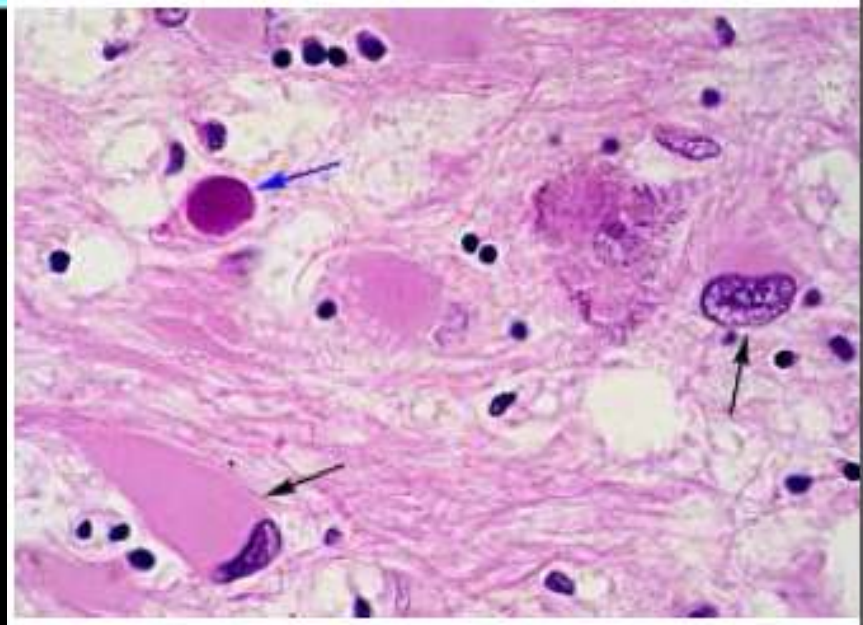


Koralnik IJ, et al. Neurology 1999
De Luca A et al. AIDS 2008

JCV PML TANI

- Serolojik testler
  - Tanıda yararı yok
  - Toplumda seropozitiflik yüksek

- Kesin tanı
  - Beyin biyopsisi
  - İntranükleer inklüzyonları olan oligodendrositler, miyelin kaybına eşlik eden büyük dismorfik astrositler ve lipid dolu makrofajlar
  - İmmünohistokimyasal boyalarla JC virüsün gösterilmesi



H-E Boyama, siyah ok; reaktif astrosit, mavi ok; geniçlemiş oligodentrosit

JCV TEDAVİ

- Spesifik tedavisi yok
- PML tanısı konulan ve tedavi almayan HIV hastasına hızla ART başlanmalı
- ART aldığı halde PML tanısı konulan ve HIV viremisi olan hastalarda tedavi gözden geçirilmeli (uyumsuzluk?, direnç?)

JCV TEDAVİ

- Citarabin in vitro JCV replikasyonunun önlüyor, klinik kullanımda etki ?
- Cidofovir in vitro SV 40 ve murine Polyomavirüs'e etkili ancak BKV ve JCV'ye etkisi net değil, klinik kullanım tartışmalı
- Mirtazapin (Remeron), 5-HT2A reseptör blokeri ?
- Meflokin, hücre kültüründe JCV replikasyonunuönlüyor, klinik çalışmalarda etkisiz
- IRIS ilişkili PML'de metilprednisolon

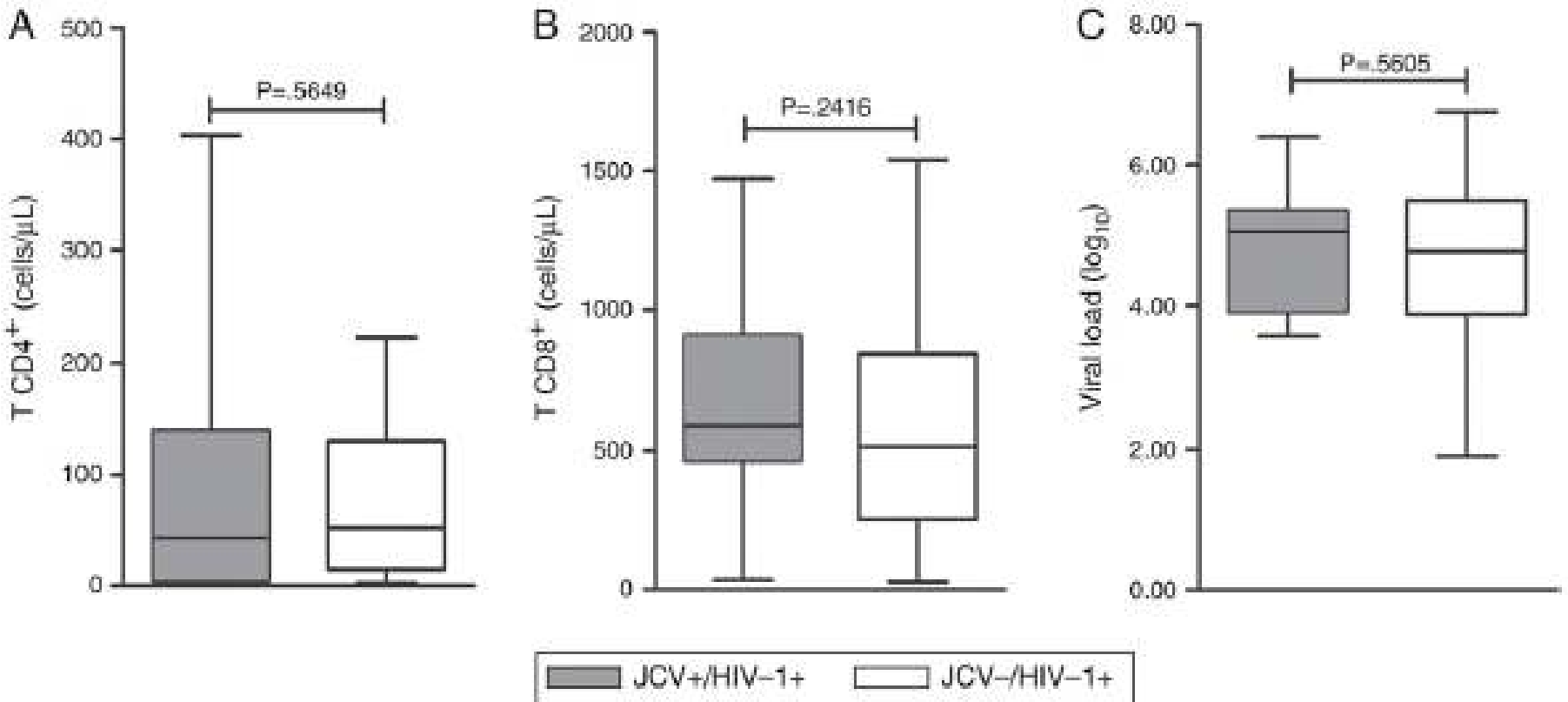
De Luca A, et al. Neurology 1999
Masur H, et al,. Clin infect. Dis. 2014
Brew BJ, et al. Nat Rev Neurol 2010
Travis J, et al. Neurologist 2010

JCV PROGNOZ

- Çoğu olgu fatal
- ART öncesi 1 yıldan uzun yaşam %10, ART sonrası %50
- Humoral immün yanıt hastalığı önlemez
- Hücresel immün yanıt çok önemli
- PML lezyonlarında bir inflamasyon göstergesi olan miyoinositol yüksekliği iyi prognoz
- CD4 sayısı <100 hücre/mm3 olanlarda mortalite oranı yüksek

- 66 HIV-1 (+) hasta
- 50 mL idrar alınarak JCV PCR
- 21hastada (%32)JCV PCR (+)

Cayres-Vallinoto IMV, et al. Braz jinfect dis 2016



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Research Report

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DOI: 10.1177/0300060517746289
journals.sagepub.com

Detection a analysis of variants o polyomavirus in urine ples from HIV-1-in ed patients in China's iang Prov

Caiqin Hu*, Ying Huang*, Junwei S
Mengyan Wang, Qihui Zhou and B

Abstract

Objectives: Human JC polyomavirus (JCPyV) in progressive multifocal leukoencephalopathy (PML). lence with which they cause PML. Currently, the JCl in patients with human immunodeficiency virus-1 (H aimed to investigate the epidemiology and subtyp patients in China.

Methods: Urine samples from 137 HIV-1-infected pa tested for the presence of JCPyV DNA. The detected using BioEdit and MEGA software.

Results: Among urine samples from HIV-1-infected patients, 67.2% were positive for JCPyV DNA (92/137). Primarily, the type 7 strains of JCPyV were detected, among which 45.5% (15/33) were subtype 7A, 30.3% (10/33) were 7B, and 24.2% (8/33) were 7C. Six nucleotide mutations, as well as one amino acid substitution, were isolated from the patients.

Conclusions: Urine samples from HIV-1-infected patients from Zhejiang Province show a high JCPyV infection rate. The most common JCPyV strains are subtypes 7A, 7B, and 7C.

Category	Total	JCPyV-negative patients	JCPyV-positive patients	P-value
Overall, n (%)	137	45 (32.8)	92 (67.2)	0.477[1]
Sex, n (%)				
Male	121	41 (33.9)	80 (66.1)	0.274[2]
Female	16	4 (25.0)	12 (75.0)	
Age, years, n (%)				
≤20	1	1 (100)	0 (0.00)	0.276[1]
21–40	88	29 (33.0)	59 (67.0)	
41–60	35	10 (28.6)	25 (71.4)	
>60	13	5 (38.5)	8 (61.5)	
CD4+ cells/mm^3, n (%)				
<200	55	21 (38.2)	34 (61.8)	
≥200	82	24 (29.3)	58 (70.7)	

and analysed

TEŞEKKÜR EDERİM…