Journey of an Immunocompromised Patient

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A VERY immunocompromised patient…

A [redacted] Y [redacted] from [redacted], with hypogammaglobulinemia since childhood, dx'ed with common variable immunodeficiency (CVID) at age 14

Came to the US in Jan 2000 and established care with Stanford Immunology

- GENETIC TESTING noted homozygous mutation of ICOSLG gene.

→ **Deficiency of the ICOS/ICOS-ligand pathway**

ICOS/ICOS Ligand Pathway

- ICOS belongs to the family of costimulatory T cell molecules
- ICOS:ICOS-L interaction is critical for the activation, proliferation and differentiation of T cells and B cells

Patients with ICOS/ICOS-L deficiency

- Initially identified w/ hypogammaglobulinemia with recurrent bacterial infxn

  → "**CVID**"

- Now noted additional risk for infxn 2/2 T cell dysfunction (e.g., HPV, *Cryptococcus*)

  → Combined Immunodeficiency (**CID**)

An immunocompromised pt with ICOS-L deficiency

- On IVIG since 2003
- Notable for:
  - Severe cytopenias w/ significant hepatosplenomegaly
  - Chronic hepatitis, “autoimmune-like”
    - CVID: ~ 50% pts w/ liver dz (*Pecroaro et al. Front Immun 2020)*
    - For ICOS deficiency, ~20% w/ hepatomegaly and abnl LFTs *(Schepp et al. Front Immunol. 2017)*
- Similar disease affected 2 other siblings and 1 cousin – all deceased

An immunocompromised pt with ICOS-L deficiency

Known recurrent infections with:

- Giardia
- UTI, pyelonephritis, prostatitis
- Sinusitis/bronchitis/PNA
- Bacterial conjunctivitis
- Oral thrush, cutaneous fungal infections
- Herpes zoster

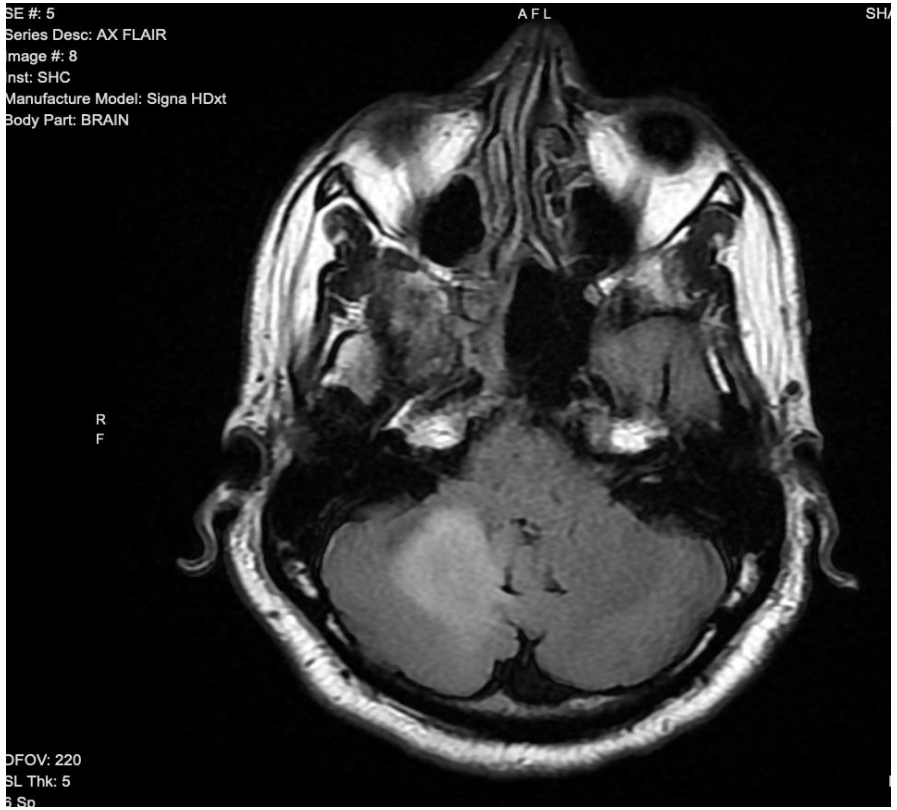
An immunocompromised pt with ICOS-L deficiency

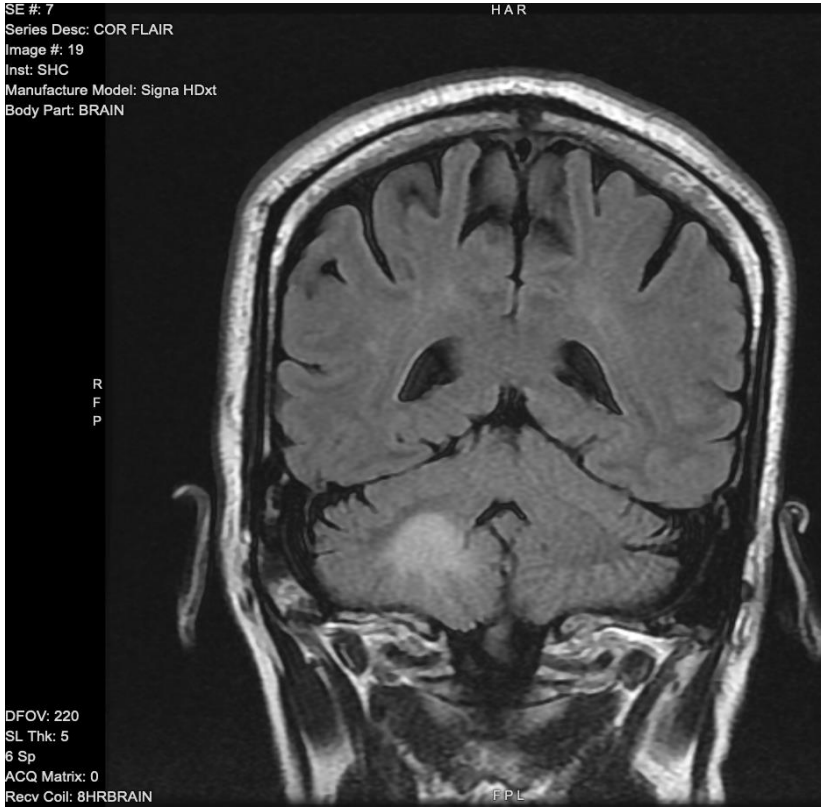
- [redacted] 2019, presented to OSH with new onset “dizziness”
  - Problems with balancing and typing, shaking

- MRI noted 2.8 x 3.3.cm R cerebellar lesion

  →Transferred to Stanford

[redacted]/[redacted]/19 MRI (OSH)





Brain Lesion?

- LP performed
- **CSF:**
  - Colorless, clear, 1 WBC, 4 RBC; normal protein/glucose
  - Meningitis/encephalitis panel negative
  - Gram stain negative; Culture no growth
  - MTB PCR neg
  - Toxo PCR neg

- ID team was asked to treat “empirically”

Quiz #1

- If you were to treat this patient “empirically”, what would you give?

a) Nothing; call Oncology
b) Vancomycin + ceftriaxone + ampicillin
c) TMP-SMZ + imipenem
d) Foscarnet +/- (b)
e) Ambisome +/- (b)
f) Sulfadiazine + pyrimethamine (+ folinic acid)

Brain Lesion?

- LP performed
- CSF: unremarkable… until

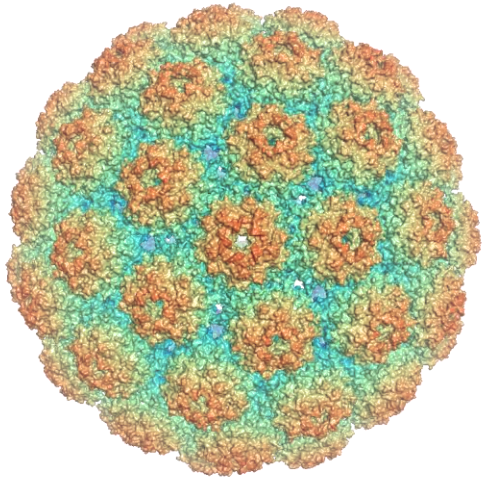
  → JC PCR positive

Clinical diagnosis:

Progressive multifocal leukoencephalopathy (PML)

associated with **JC Polyomavirus (JCPyV)**

Polyomavirus



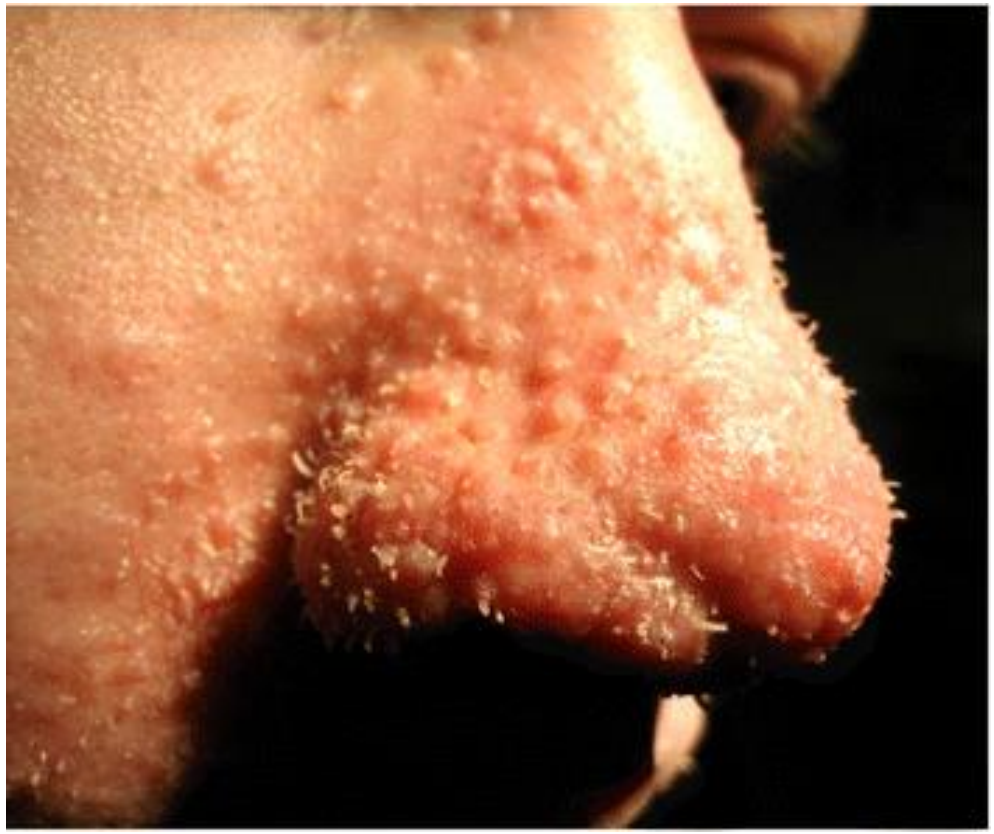
- First isolated in 1952 in mice
- A small, non-enveloped, ds-DNA virus w/ an icosahedral capsid
- Circular genome of ~ 5.5 kbp, encoding 5-9 proteins
- Cells infected with murine polyomavirus induced multiple (*poly*) tumors (*omas*) in immunocompromised mice
- Now 117 species recognized; 14 known to infect humans

13 Known Human Polyomaviruses (Ref: Assetta & Atwood; Bio Chem 2017)

Full name	Abbreviation	Source of isolation	Year of discovery	Disease caused
BK polyomavirus	BKPyV	Urine	1971 (Gardner et al., 1971)	Polyomavirus associated nephropathy (PyVAN), hemorrhagic cystitis (HC)
JC polyomavirus	JCPyV	Urine, brain	1971 (Padgett et al., 1971)	Progressive multifocal leukoencephalopathy (PML)
Karolinska Institute polyomavirus	KIPyV	Nasopharyngeal tissue	2007 (Allander et al., 2007)	None
Washington University polyomavirus	WUPyV	Nasopharyngeal tissue	2007 (Gaynor et al., 2007)	None
Merkel cell polyomavirus	MCPyV	Skin lesions	2008 (Feng et al., 2008)	Merkel cell carcinoma (MCC)
Human polyomavirus 6	HPyV6	Skin	2010 (Schowalter et al., 2010)	None
Human polyomavirus 7	HPyV7	Skin	2010 (Schowalter et al., 2010; Ho et al., 2015)	Pruritic rash (2 cases)
Trichodysplasia spinulosa-associated polyomavirus	TSPyV	Skin lesions	2010 (van der Meijden et al., 2010)	Trichodysplasia spinulosa
Human polyomavirus 9	HPyV9	Blood, skin, urine	2011 (Scuda et al., 2011)	None
Malawi polyomavirus	MWPyV	Stool	2012 (Buck et al., 2012)	None
St Louis polyomavirus	STPyV	Stool	2012 (Lim et al., 2013)	None
Human polyomavirus 12	HPyV12	liver, cecum, rectum, stool	2013 (Korup et al., 2013)	None
New Jersey polyomavirus	NJPyV	muscle, skin	2014 (Mishra et al., 2014)	Muscle and ocular damage (1 case)

Trichodysplasia spinulosa

- A rare skin disease that mainly affects immunocompromised pts (e.g., organ transplant recipients)



Naldi et al. Clin Rev Allergy & Immuno 2018; 54(3)

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Human polyomavirus 12	HPyV12	liver, cecum, rectum, stool	2013 (Korup et al., 2013)	None
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The 14th human PyV identified - Lyon IARC polyomavirus, isolated from human skin *(Gheit et al. Virology 2017; 506:45-54)*

JC Polyomavirus

- First identified as the causative agent of PML in 1971 when isolated from the brain tissue of pt John Cunningham
- Ubiquitous; seroprevalence ~40-80%
- Transmission: primarily fecal-oral
- Primary infection (asymptomatic) → hematogenous spread to other organs/tissues → latency in urological tissues
- Healthy subjects: ~20% shed JCPyV in urine

JC Polyomavirus

- High prevalence of JCPyV infection, but PML is very rare
- To develop PML, certain form of immunosuppression is a sine qua non, with very rare exceptions

How does JCPyV go from “benign” infection to life-threatening CNS infection?

Proposed Stages of PML Pathogenesis:

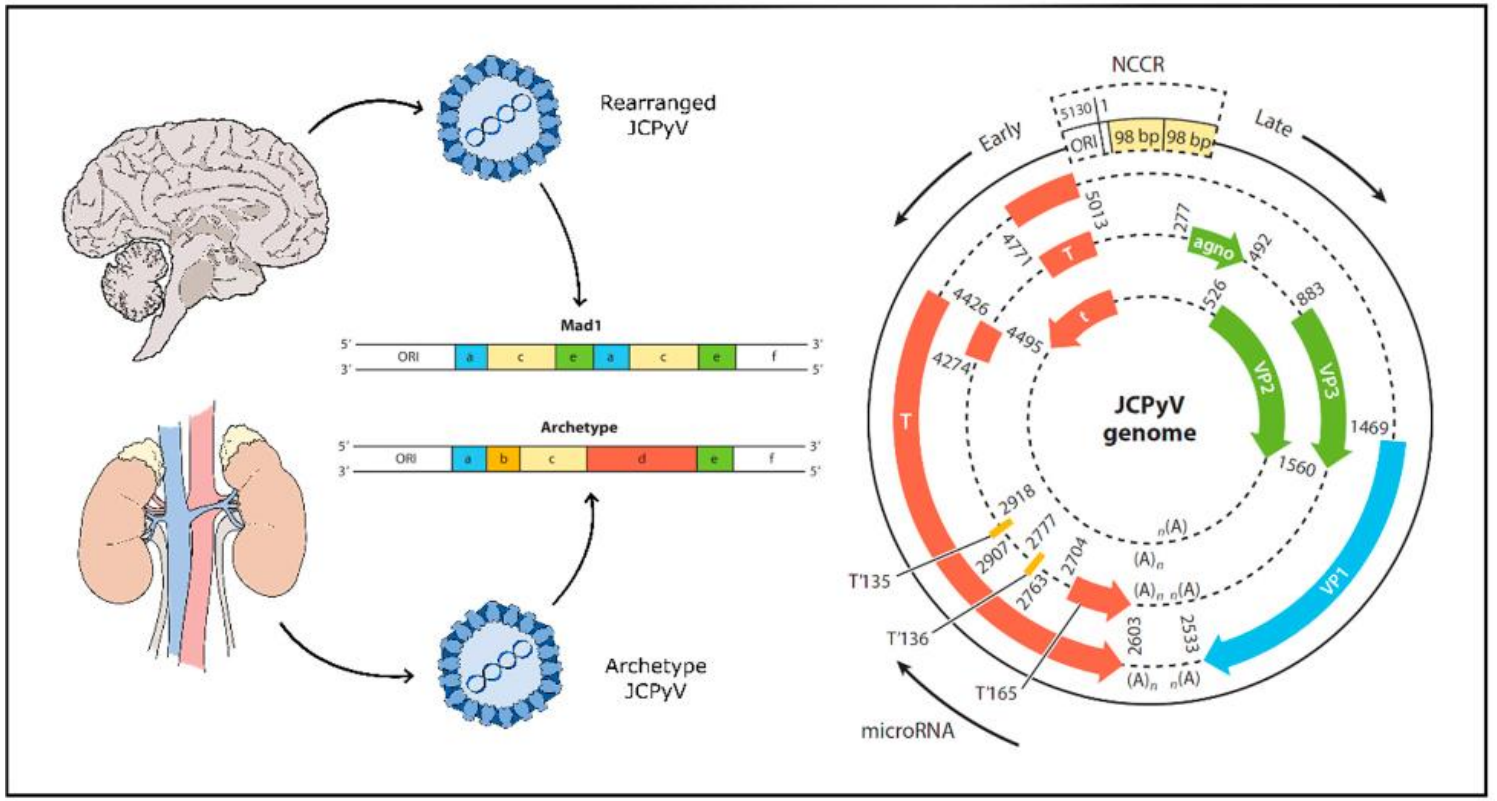
Non-pathogenic archetype JCPyV establishes latent infxn in kidney or other sites.

→ Prolonged/profound immunodeficiency allows viral reactivation/replication

→ Genetic rearrangement → emergence of neurotropic PML-type.

→ Entry into the brain → productive infection of glial tissues.

→ Failed CNS immunosurveillance allows development of PML and/or other forms of CNS infxn.



Atkinson & Atwood 2020; Viruses Vol. 12 Issue 9

JC Polyomavirus

Neurologic diseases associated with JCPyV:

- **Progressive multifocal leukoencephalopathy (PML)**
- JCPyV cerebellar granule cell neuropathy
- JCPyV meningitis
- JCPyV encephalitis
- JCPyV-associated encephalopathy

A Brief History of PML

First recognized in 1958 among pts with primary B cell malignancies.

- Of 230 cases reported 1958 -1984:
  - ~70%: Lympho- or myelo-proliferative disease
  - ~23%: Others form of immunodeficiency or inflammatory state

    E.g., Renal transplant, SLE, sarcoidosis, etc. *(Brooks, 1984).*

HIV/AIDS pandemic in early 1980's → drastic change of the PML epidemiology

- First case of PML w/ AIDS in 1982 *(Miller, 1982)*
- ~ 5-10% of HIV pts would develop PML *(Adang, 2015)*
- Introduction of HAART → significant decline of PML prevalence, although AIDS remains the most common predisposing cause of PML in the US *(Rocchi, 2023)*

A Brief History of PML:

Latest recognized predisposing condition: Certain biologics

Natalizumab

- Targets vα4β1 and α4β7 integrins

  → inhibits leukocyte entry into CNS via VCAM-1 (and GI tissues via MAdCAM-1)

- FDA approved in 2004 for MS → Removed from market voluntarily in 2005 w/ 3 cases of PML → Re-introduced into the American market in 2006 *(Shirani, 2018)*

Efalizumab

- Targets anti-CD11α, the alpha-subunit of the β2-integrin (LFA-1).
- → inhibits leukocyte trafficking through the vasculature to areas of tissue inflammation.
- FDA approved in 2005 for severe plaque psoriasis → Removed from market in 2009 w/ 3 fatal cases of PML

The estimated risks of PML with efalizumab was 1:400, as cpd to 1:1000 with natalizumab. (Carson 2009)

Biologics with PML Risks

Immunomodulator Targets	Agents with PML Risks	Labelled warning on package insert	Cases published in the literature
Cell surface receptors and associated signaling pathway inhibitors			
α4β1-integrin	natalizumab	√ (Boxed warning)	√
α4β7-integrin	vedolizumab	√	*
Sphigosine-1-phosphate receptor	fingolimod	√	√
	ozanimod	√	√
	ponesimod	√	*
	siponimod	√	√
Agents targeting lymphoid or myeloid cell surface antigens			
CD19 + CD3	blinatumomab		√
CD20	rituximab	√ (Boxed warning)	√
	ofatumumab	√	√
	ocrelizumab	√	√
	obinutuzumab	√ (Boxed warning)	√
CD30	brentuxumab vedotin	√ (Boxed warning)	√
CD38	daratumumab		√
CD52	alemtuzumab	√	√
CD79b	polatuzumab	√	*
CD80/CD86-CD28	belatacept	√	√
CD319	elotuzumab		√
BAFF	belimumab	√	√

Immunomodulator Targets	Agents with PML Risks	Labelled warning on package insert	Cases published in the literature
Intracellular molecule and signaling kinase inhibitors			
Bruton's tyrosine kinase	ibrutinib	√	√
PI3K	idelalisib		√
JAKs	ruxolitinib	√	√
mTOR	sirolimus	√	√
	tacrolimus	√	√
Ubiquitin proteasome	bortezomib	√	√
	carfilzomib	√	√
	ixazomib		√
Agents targeting cytokines and their signaling pathways			
TNF-alpha	Infliximab		√
	adalimumab		√
	etanercept		√
IL-2R (CD25)	basiliximab		√
IL-6R	tocilizumab		√
Agents targeting the complement system			
C5	eculizumab		√

* No cases reported in the literature to date.

PML: What are other predisposing conditions?

- Malignancy - lymphoproliferative and myeloproliferative diseases
- HIV- most common predisposing condition
- Certain biologics
- HSCT and SOT
- Autoimmune disorders
  - Up to 23% of PML cases
  - Highest risk with SLE; also RA, vasculitis, dermatomyositis, sarcoidosis, etc.
  - Underlying condition vs immunosuppression?
- Primary immunodeficiency disorders
  - E.g., idiopathic CD4 lymphocytopenia, GOF STAT 1 deficiency
- Isolated cases in the absence of “known” immunodeficiency
  - Review of 38 cases, 7 (18.4%) with **liver cirrhosis**, 5 (13.2%) with renal failure, 5 (22.7%) with low CD4+ T cells *(Gheuens et al J Neurol Neurosurg Psychiatry. 2010;81(3):247.)*

Clinical Manifestations:

Classic PML:

- May be asymptomatic in the very early stage
- Subacute presentation – symptoms vary depending on the location of CNS lesions
  - E.g., AMS, motor deficits, limb/gait ataxia, visual symptoms (hemianopia and diplopia)

Inflammatory PML (PML - IRIS)

- New onset or clinical worsening

  e.g., HIV pts started on ART, withdrawal of natalizumab

  → marked increase in CD4+ T-cells and immune recovery

Clinical Manifestations

Other JCPyV-associated neurologic diseases have varying presentations:

- JCPyV cerebellar granule cell neuronopathy
  - Infects cerebellar neurons, not glial cells → Cerebellar atrophy
- JCPyV encephalopathy
  - Infects cortical pyramidal neurons, gray matter with limited demyelination
- JCPyV meningitis
  - Infects leptomeningeal and choroid plexus cells, and limited parenchymal involvement

Diagnosis

Neuroimaging

- Focal or multifocal white matter lesions without mass effect, that do not conform to vascular territories.

CSF

- JCPyV PCR: Sensitivity 72->95%; Specificity 92-100%
- WBC < 20 cells/mcL; Protein <100 mg/dL
- A negative PCR does NOT rule out PML

Brain biopsy

- Gold standard; sensitivity 64-96%, specificity 100%
- **Triad:** demyelination, bizarre astrocytes, and enlarged oligodendroglial nuclei

  → confirmed by IHC
- Usually devoid of inflammatory infiltrates, except PML-IRIS

PML: Prognosis

- HIV population – significantly improved with HARRT
  - 1-year survival increased from 10% to >50%
  - Median survival increased from 0.4 to 1.8 years
- Non-HIV populations
  - Case-fatality rate up to 90%
  - Median survival – 2 months *(Neil et al. Bld Adv 2017)*
- In one recent study of 47 pts comparing non-HIV vs HIV *(Kim et al. Sci Report 2023):*
  - Median survival: 184 vs. 1,564 days
  - 1-year mortality rates: 60.0% vs. 25.9%,
  - Overall mortality rates: 80.0% vs. 40.7%

Back to Our Patient:

April 2019: Admission for R cerebellar lesion, found to have JC-associated PML

- Noted rapid progression
- **DC Summary:** “The patient's prognosis is poor with average survival in the order of months from time of diagnosis…”

Quiz #2

- How would you treat this patient?

a) Nothing to offer; call Palliative Care Team
b) Mirtazapine +/- IVIG
c) Cidofovir
d) IFN a +/- b
e) Pembrolizumab
f) Virus-specific T cell therapy

Management of PML

Strategies:

Immune reconstitution

1. Discontinue or reduce immunosuppression if possible
2. Start or maximize ART for HIV/AIDS
3. Discontinue specific offending drug (e.g., natalizumab)

   +/- plasma exchange or immunoadsorption

- Noted PML-IRIS may occur, especially with (2) and (3)

Management of PML

Direct or indirect antivirals:

- **Cytarabine** – nucleoside analogue
- **Cidofovir** – nucleotide analogue
- **Topotecan** – topoisomerase inhibitor
- **Mirtazapine** – antagonist of serotonin receptor 5-HT2R

  → plays a role in multiple stages of JCPyV infection - viral attachment to later trafficking within endosomes
- **Mefloquine** – via 5-HT2R? *(Thompson AJ, Br J Pharmacol 2007; Yoon S, Encephalitis 2021)*

Management of PML

Modulating the immune system:

- **Filgrastim**
- **IL-7**
- **Interferon α and β**
- **Maraviroc –** for PML-IRIS (inhibits CCR5+ receptor and enhance CD4+T-cell recovery)

Management of PML

Direct or indirect antivirals:

- Cytarabine
- Cidofovir
- Topotecan
- Mirtazapine
- Mefloquine

Modulating the immune system:

- Filgrastim
- IL-7
- Interferon α and β
- Maraviroc

Most with mixed results; none of these are considered very effective.

Management of PML

Improving the immune system against JCPyV:

- **Checkpoint inhibitors:**
  - Nivolumab
  - Pembrolizumab
  - Atezolizumab

- Evidence: Mixed outcomes

Review of PML Cases Treated with CPIs - Treatment and Outcome of 79 Pts

(Modified from Boumaza Ann Neurol 2023)

Underlying Disease		All	Hematologic Malignancies	Primary Immuno-deficiencies	HIV/AIDS	Chronic Inflammatory Diseases	Solid Malignancies	Transplant Recipients
Number of pts		79	38	14	12	8	5	2
Checkpoint Inhibitors	Nivolumab	24	9	6	5	1	1	2
	Pembrolizumab	53	28	8	7	7	3	0
	Atezolizumab	2	1	0	0	0	1	0
Additional Rx	Mirtazapine	25	7	5	8	2	1	2
	Mefloquine	6	2	2	0	2	0	0
	IVIg	5	2	2	0	1	0	0
Survivors at 12 months		41 (51.9%)	19	8	6	5	0	0
Death from any cause		38 (48.1%)	19	6	6	3	2	2
Death from PML		**26 (32.9%)**	15	4	2	1	2	2
Death from PML-IRIS		**7 (8.9%)**	3	-	2	2	-	-
Death from PML & underlying condition		**3 (3.8%)**	-	1	2	-	-	-
Death from underlying condition		2 (2.5%)	1 (2.6%)	1 (7.1%)	-	-	-	-

Management of PML

Improving the immune system against JCPyV:

- Checkpoint inhibitors
- Viral specific T-cells against JCPyV

Virus-specific T cell therapy for PML

A proof-of-principle study - Muftuoglu et al of MD Anderson (NEJM 2018):

- Use ex vivo-expanded, partially HLA-matched, third-party–produced, cryopreserved BK virus–specific T cells
  - Pt 1: cord-blood tx for AML

    → complete clearance of JC in CSF; resolution of clinical and imaging findings → asymptomatic
  - Pt 2: polycythemia rubra vera on ruxolitinib

    → reduction of JC in CSF by 2.5 logs, s/sx static → chose hospice and died 8 months later
  - Pt 3: HIV/AIDS, off HAART; PML progressed despite restarted on HAART

    → complete clearance of JC in CSF → improvement of clinical and radiographic findings

Virus-specific T cell therapy

A recent review – Lambert et al (Viruses 2023):

- 4 case reports and 5 case series → **34 pts total**
- BK-specific T-cells (n = 22); JC-specific T cells (n = 12)
- Cause of immune deficiency:
  - Heme malignancy (n = 23; including 9 s/p allo-HSCT and 10 s/p auto-HSCT)
  - Primary immunodeficiency (n = 5)
  - Autoimmune disease (n = 3),
  - HIV (n = 1); SOT (n = 1); chronic HBV (n = 1)
- **Outcome:**
  - 21 = favorable clinical course: Improved (n = 16); Stabilized (n=5)
  - 11 = deteriorated and died of PML
  - 2 = IRIS
- Average time between PML dx and 1st T-cell infusion = 2.6 months → potential selection bias excluding the most impaired patients.

Back to Our Patient:

[redacted] 2019 Admission for R cerebella mass, found to have JC-associated PML

- **Assessment:** Poor prognosis, except survival in the order of months from time of diagnosis
- Pembrolizumab was considered – “Some concern about adverse effects…, including possible worsening of his autoimmune hepatitis.”

→ Patient was discharged on mirtazapine

Back to Our Patient:

- Referred to MD Anderson for a clinical trial to receive BK virus-specific T cells.
- First infusion performed ~ 6 wks after DC

Back to Our Patient:

- June: CSF JCPyV titer = 375
- June: Infusion #1
- July: MRI showed improvement
- July: Infusion #2
- August: JCPyV undetectable
- August: Infusion #3
- September: Stanford Immunology clinic visit→ able to walk short distance
- October: JCPyV undetectable
- November: JCPyV undetectable

Life after PML …

- Suffering from chronic diarrhea with **norovirus**
- Failed 2 courses of nitazoxanide (2019, 2022)
- Fecal transplant in [redacted] 2024
- Stool cleared of Norovirus by [redacted] 2024

Life after PML and Norovirus…

- Admitted [redacted] 2024 for decompensated liver failure (worsening jaundice and ascites)

→ **Liver Transplant?**

Quiz #3

- Would you “clear” the patient to proceed with Liver Transplant?

a) No, too high risk
b) Yes, with transplant protocol per routine
c) Yes, with close monitoring with JC PCR (Blood)
d) Yes, but need “minimal” immunosuppression post transplant
e) (c) + (d)

Life after PML and Norovirus…

Per MD Anderson,

> *"… should he be a candidate for liver transplant, the risk of PML recurrence is thought to be very low. As a contingency, he can return to MD Anderson for repeating the T cell adoptive therapy if he has a recurrence."*

Life after PML and Norovirus…

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- **Underwent OLT [redacted] 24**
- Recovered well and discharged on POD#11

Life after PML, Norovirus and OLT…

After OLT:

Post-op course: CMV viremia (CMV status D+/R+)

- (Val)ganciclovir Rx complicated by pancytopenia

  → letermovir as PPX

- On IVIG q5 wks for CVID
- Clinically doing quite well

Now back to work full time!