Research Square

Preprints are preliminary reports that have not undergone peer review.
They should not be considered conclusive, used to inform clinical practice,
or referenced by the media as validated information.

Fatal JC-virus Granular Cerebellar Neuronopathy associated with Autoimmune Lymphoproliferative Syndrome and Common Variable Immunodeficiency

Jannik Helweg-Larsen (jannik.helweg-larsen@regionh.dk)
Rigshospitalet https://orcid.org/0000-0001-7192-0144
Morten Rasmussen
Statens Serum Institut
Maiken Rosenstierne
Statens Serum Institut
Jakob Thaning Bay
Rigshospitalet
Lise Mette Rahbek Gjerdrum
Zealand University Hospital: Sjaellands Universitetshospital Roskilde
Regitze Bangsgaard
Rigshospitalet
Peter Gideon
Rigshospitalet
Rasmus L. Marvig
Rigshospitalet
Finn Selleberg
Rigshospitalet Neurocentret
Hanne Vibeke Marquart
Rigshospitalet
Lars Peter Ryder
Rigshospitalet
Anders Fomsgaard
Statens Serum Institut
Daniel Kondziella
Rigshospitalet Neurocentret

Research

Keywords: JC-virus associated granular cerebellar neuronopathy, Progressive multifocal leukoencephalopathy, Autoimmune lymphoproliferative syndrome, CVID, PD-1 inhibitor treatment,

Opportunistic infection

Posted Date: September 30th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-81384/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License

Abstract

Background: JC-virus (JCV) associated granular cerebellar neuronopathy (JCV-GCN), which causes severe ataxia, is a rare complication of severe immunodeficiency and caused by a variant of JCV with a VP1-deletion. JCV-GCN has not yet been reported in patients with autoimmune lymphoproliferative syndrome (ALPS-FAS). We report a 34-year old woman with autoimmune lymphoproliferative syndrome (ALPS-FAS) and common variable immunodeficiency (CVID) who developed JCV-GCN which progressed to fatal *progressive multifocal leukoencephalopathy (*PML).

Methods: Extensive longitudinal virologic, genetic and immunologic characterisation by JCV CSF quantification and sequencing, peripheral blood flowcytometry and exome sequencing.

Results: A diagnosis of JCV-GCN was established by findings of severe cerebellar vermis atrophy on MRI and a JCV variant with a VP1-deletion (JCV-VP1) in CSF. During a period of 18 months, at which treatment with high dose immunoglobulin, cidofovir, mirtazapine and high dose fucidic acid were given, cerebellar ataxia was relatively stable. In CSF a mixture of predominantly JCV-VP1 with only low levels of wildtype JCV was found. However, classic PML ensued, with rising JCV- CSF levels and a complete change to JCV-wildtype quasi species without JCV-VP1. Immunological findings were unusual, with disappearance of the original ALPS-FAS phenotype. Trio-exome sequencing identified a heterozygote de novo variant of unknown significance in *RAG1.* FAS mutations were not detected in the patient or in the parents, suggesting that her previously diagnosed ALPS-FAS-FAS was caused by somatic mosaicism. At the progression to PML, increased expression of T-cell PD-1 was demonstrated, suggesting T-cell exhaustion. Treatment with pembrolizumab, an inhibitor of PD-1, was attempted but followed by rapid and fatal PML progression.

Conclusion: JCV-GCN may complicate ALPS and may progress to PML. In JCV-GCN, wild-type and JCV-VP-1 can co-exist in CSF. Quantification and sequencing of JCV in CSF is helpful to characterize and monitor disease and treatment. Progression of disease may be associated with development of T-cell exhaustion, but the benefit PD-1 inhibitor treatment is uncertain.

Background

In immunocompromised patients, the primary disease caused by reactivation of JCV is PML. JCV affects the white matter of the brain by productive and lytic infection of oligodendrocytes and astrocytes. However, in 2003 a rare syndrome caused by productive and selective infection of cerebellar granule cell neurons by a JCV variant with a small deletion in the VP1 capsid was described (1–3).

Autoimmune lymphoproliferative syndrome (ALPS-FAS)

Autoimmune lymphoproliferative syndrome (ALPS-FAS) is characterized by FAS gene mutations that leads to defective lymphocyte apoptosis with uncontrolled proliferation of lymphocytes accompanied by autoimmune cytopenia, splenomegaly, lymphadenopathy and increased risk of lymphoma (4). ALPS-FAS

was first characterized in the 1990'ies in patients with chronic lymphoproliferation and an increased number of a characteristic "double negative T cells (DNT)". Germ-line FAS mutations is the most common cause of ALPS-FAS, but it can also be caused by somatic FAS mutations (10%) (5). The disease has variable penetrance and severity. In the largest cohort study of ALPS-FAS, patients had relatively good prognosis (estimated survival by age 50, 85%) but a high risk of post-splenectomy sepsis and lymphoma. In this cohort opportunistic infection was rare and typically associated with immunosuppressive treatment of autoimmunity (6). A subset of ALPS-FAS patients with ALPS-FAS have associated CVID, which may be difficult to distinguish in clinical practice.

Methods

Extensive longitudinal virologic, genetic and immunologic characterisation by JCV CSF quantification and sequencing, peripheral blood flowcytometry and exome sequencing.

Results

A 34-year old woman was diagnosed at early childhood with a primary immunodeficiency presenting with autoimmune hemolytic anemia (AIHA), hypogammaglobulinemia, lymphadenopathy, recurrent upper respiratory infections and meningitis. After splenectomy for AIHA, she continuously received intravenous immunoglobulin substitution, during which infections were relatively infrequent. At the age of 13 years flowcytometry revealed an increased fraction of CD4/CD8 double negative T-cells (DNT), comprising between 30–50% of the TCRab CD3 positive T-cells. Based on these findings a defect in FAS induced apoptosis was suspected. At the age of 14 a missense Ile243-Arg FAS mutation (laboratory of Rieux-Laucat, Paris) was verified in peripheral blood cells. Based on these findings and reduced mutated fraction of somatic hypermutation of expressed immunoglobulin kappa light chain (examined by restriction enzyme based hot-spot mutation assay (IgκREHMA)) in B-cell, a definitive diagnosis of ALPS-FAS with CVID was made (7).

During her lifetime she had persistent moderate neutropenia and normal serum B12 levels. T-cell lymphocytosis, up to 18 mia/L CD3 positive T-cells consisted of up to 60% DNT, was detected regularly up to the age of 18 (2002) but at the age of 26 (2010) a significant decrease of T-cell lymphocytosis and DNT fraction was observed.

At age of 27 years, she was treated for recurrent genital HPV condylomata. Two years later, progressive extensive bluish nodular skin lesions developed Fig. 1. Cutaneous lymphoma was suspected, but skin biopsies demonstrated a polyclonal T-cell lymphoproliferation and lymph node biopsy and PET-CT were without lymphoma. Treatment with alitretinoin followed by 6 months of peg-interferon had no effect on the skin lesions.

Early 2017, at age 34, she developed slowly progressive gait disturbance and vertigo, which during the next 6 months progressed to severe truncal ataxia, dyskinesia and nystagmus. Cognition was normal.

Severe cerebellar vermis atrophy was found on MRI. Figure 2, A and B. CSF was acellular with normal protein. Extensive investigations for infectious, autoimmune and paraneoplastic conditions were done on CSF and blood including gastrointestinal biopsies and whole-body PET-CT, which were all negative. High dose high dose iv methylprednisolone was given on suspicion of an auto-inflammatory aetiology but stopped when CSF was found positive for JCV DNA. A diagnosis of JCV-GCN was made.

Treatment

IVIG treatment doses were increased to keep IgG at a minimum level of 12 g/l. Mirtazepin, which she already received for depression, was continued.

Cidofovir treatment was initially given 7 times for three months (September to November 2017), during which cerebellar symptoms and MRI changes were stable and CSF-JCV levels decreased moderately- Fig. 3. Three months later, however, progression was suspected because of slight worsening in ataxia and rising JCV-CSF levels, at which time cidofovir treatment was repeated once, but was terminated because of uveitis, possibly related to cidofovir(8) .

Fusidic acid, commonly used in Denmark for treatment of staphylococcal infections, has possible *in vitro* efficacy against JCV with a single case report describing effect against JCV associated nephropathy(9,10). In standard dosage, fusidic acid has relative low CSF penetration, but better into brain tissue(11–13). Since progression of ataxia was suspected and CSF-JCV-levels remained (Fig. 2), treatment with high dose fusidic acid (1500 mg x 2) was attempted. After 1 month at which a relatively high level of CSF-fucidic acid (2.5 mg/L) was measured JCV-CFS levels had decreased to 71 from 478 copies/ml. Because of gastrointestinal side-effects, the dosage was then reduced to 500 mg x 3 after which CSF-fucidic acid levels decreased to 0.4 mg/L, after which time treatment was stopped, Fig. 3. During the next 7 months, the ataxia, MRI and skin changes remained unchanged. JCV was detected twice in blood.

However, over a 2-week period in November 2018, she suddenly developed progressive severe blindness and reduced lower leg power. On MRI non-enhancing parietal PML lesions was found bilaterally- Fig. 2. PML is associated with increased programmed cell death-1 (PD-1) expression, a marker of cellular immune exhaustion with increased JCV-specific T-cell immune responses following PD-1 inhibition(14). At the change from JCV-GCN to progressive PML, increased PD-1 expression on T-cells was demonstrated. Based on these observations and a case report showing benefit of PD1- inhibition in BK-encephalitis (Holland SM, oral presentation, ESID, Barcelona 2016, unpublished. Subsequent reports of PD-1 inhibitor treatment of PML had not been published), we decided to administer the PD-1 inhibitor pembrolizumab.

However, 5 days after pembrolizumab infusion she developed severe encephalopathy with confusion and a central fascial paresis. Although no definitive signs of IRIS could be demonstrated on MRI, PD-1 inhibitor associated immune reconstitution inflammatory syndrome (IRIS) encephalitis was suspected,

and methylprednisolone was administered, with only limited effect. PML progressed rapidly and she died 14 days after the pembrolizumab infusion.

Immunology

At the diagnosis of JCV-GCN (age 32) 2017, in contrast to earlier findings of T-cell lymphocytosis and increased fraction of DNT (less than 2%) could not be detected, Fig. 4. CD4 T-cells count (450 cells/μl) and neutrocyte count were moderately reduced, while the numbers of recent thymic immigrants were normal. B-cell count was markedly reduced and CD27 positive memory B-cells were absent, with markedly reduced somatic hypermutation in accordance with the CVID-like phenotype.

At time of progression from JCV-GCN to classical PML (age 33) 2018, a marked increase of PD1- positive CD4 T cells was observed (66%), suggesting T-cell exhaustion although paradoxically CD57 was not upregulated on CD4 T-cells. CD8 T-cells displayed moderate upregulation of PD-1 and marked upregulation of CD57.

Repeated biopsies from the skin lesions, were dominated by nodular dermal infiltration of T-cells devoid of B lymphocytes. T-cells displayed reduced expression of CD4, CD7, and CD8, the latter being more prevalent than CD4. Figure 1B-D. Double-negative T-cells could not be detected immunohistochemically, neither in the lesions nor in bone marrow biopsies. No clonal TCR rearrangements were detected. Interestingly, BCL2 expression was reduced indicating alterations in apoptosis signalling Fig. 1E.

By trio-exome sequencing FAS mutations were not detected in the patient or in the parents, suggesting that her previously diagnosed ALPS-FAS-FAS was caused by somatic mosaicism.

Exome sequencing identified a heterozygote de novo variant of unknown significance in *RAG1* (NM_000448.2, c.478C > T, p.R160W, 0.0006983% allele frequency in gnomAD v3).

Virology

During illness, a total of 11 lumbar punctures were obtained, in which CSF remained acellular with normal CSF-protein, glucose and lactate- Fig. 1. Ten of the CSF samples were available for JCV quantification. DNA was isolated from CSF using QiaCube isolation and the JCV copy number was determined by quantitative PCR using a JCV standard with known copy number(15). Sequencing of the C terminus of the VP1 gene was performed after amplification of CSF samples using primer pair JC_F2469 (ACAGAGGAGCTTCCAGGGGA) and JC_R2629 (AAACCAAAGACCCCTCCCCC). Sequencing was carried out using the Nextera XT DNA Library Prep Kit (Illumina Inc., San Diego, United States) on the Illumina MiSeq platform. Here, a 16 bp deletion in the VP1-gene resulting in an open reading frameshift was demonstrated. This has previously been shown to be associated with JCV-GCN, (16), Fig. 5.

During the course of disease and treatment with cidofovir, CSF-JCV levels declined gradually from August 2017 to spring 2018, with a nadir CSF- JC viremia of 71–200 copies/ml, Fig. 3. From all CSF samples during this period, a mixed population of the JCV-GCV variant and the wild-type JCV type were detected by sequencing, with a large predominance of JCV-GCN and only few copies of the wildtype JCV present

However, at the progression to fatal PML, CSF-JCV levels increased 10-fold to an average of 2000 copies/ml at which point only wildtype-JCV without JCV-GCN was detected (Fig. 3).

Discussion

We here report the first a case of ALPS-FAS/CVID associated JCV-GN. During the first part of illness, repeated CSF samples demonstrated a genotype mixture with almost complete predominance of a JCV variant, with a 16 bp deletion in the VP1-gene, associated with JCV-GN, together with low levels of wild type JCV(17). For 18 months, at which treatment with high-dose IVIG, intermittent cidofovir and high-dose fucidic acid were given, the severe ataxia remained stable and CSF-JCV levels decreased. However, a sudden switch to classic PML was observed, with progressive blindness, increasing CSF-JCV levels with a complete change from JCV-VP1 to wildtype JCV. Treatment with the PD-1 inhibitor pembrolizumab was unsuccessful and associated with rapid progressive fatal encephalopathy.

JCV associated disease primarily manifests as PML, through lytic infection of oligodendroglial cells with progressive demyelinating white matter lesions. Rarely, JCV may also selectively affect granule cell neurons, with resulting neuronal loss, gliosis and a clinical cerebellar syndrome.

PML is in frequent in patients with primary immunodeficiency, In a literature case study review, a total of 26 cases of PML complicating primary immunodeficiency disease (PID) was described of which 7 cases were associated with CVID and combined immunodeficiency (18). A recent French study, reported 11 patients with PID and PML, of which two patients had CVID, several cases were seen in connection with immunosuppressive treatments (19). CVID associated Granule Cell Neuronopathy has only been reported once, in a recent case (20). Previously, no cases of PML have been reported in patients with ALPS-FAS [6, 10–14](21).

The specific immune factors that hold JCV in check are unknown. In PID, PML is primarily associated with combined B and T cell impairment. Increased PD-1 Expression in T Lymphocytes has been observed in several patients with both AIDS- and non-AIDS associated PML, suggesting that T-cell exhaustion may be important (22).

ALPS-FAS has wide variability in clinical characteristics aamong individuals and subtypes. ALPS-FAS usually appears in childhood and may improve with age. The diagnosis of ALPS-FAS is based on clinical observation and laboratory abnormalities, including elevated DNT cells in peripheral blood.

The course of ALPS-FAS in our patient was distinctly unusual with transformation of the previous primary double negative T-cell lymphocytosis, with a classic FAS mutation to a state in which FAS-mutations and double negative T-cell lymphocytosis could no longer be detected in peripheral blood, skin or bone marrow biopsies at the diagnosis of PML. The time when disappearance of double negative T-cell lymphocytosis occurred is uncertain since immunophenotyping between 2002 and 2017 was only done once in 2011, at which a marked decline in lymphocytosis was observed, coinciding with the development of genital HPV papillomatosis. Her ALPS-FAS was probably caused by a somatic mutation leading to

mosaicism, since parents had no germline FAS mutations. The persisting immunodeficiency including CVID lead to a comprehensive genetic screening (EXOM-sequencing) revealing a heterozygous RAG1 mutation and no FAS mutation in accordance with the “disappearance” of the ALPS-FAS phenotype. A heterozygous RAG1 mutation has previously been described in a patient with adult-onset manifestation of idiopathic CD4 T-cell lymphopenia and B-cell dysfunction (23). We speculate that the heterozygous RAG1 mutation in our patient may have contributed to the T-cell as well as B-cell dysfunction, which might have been an additional risk factor in combination with the somatic FAS mutation.

Treatment options for PML are limited. JCV CSF quantification as a surrogate marker for treatment response is debated, and PCR methods are not standardized. However, overall there seems to be reasonable correlation between CSF-JCV levels and clinical treatment response (24,25).

In our patient, decreasing JCV-CSF levels and stable disease was observed in relation to cidofovir treatment. Whether this reflects treatment effect or merely could be a result of complete depletion of target cerebellar granula cells is however uncertain. Cidofovir treatment of PML remains controversial, as a pooled analysis of several small observational studies failed to show evidence of efficacy against AIDS-associated PML (26). However, several case reports in non-HIV associated PML have observed a possible benefit of Cidofovir(27–31)

After the death of our patient, 5 publications from 2019 describing a total of 12 patients, have reported beneficial effects of PD-1 inhibitor treatment in 9 PML patients, with increased JCV-specific T-cell immune responses(24,32–35). In the NIH study, 5 of the 8 patients had clinical improvement or stabilization, with MRI showing stabilization or reduction in lesion burden and viral load reductions in CSF(24). The remaining 3 patients had no clinical benefit. Immune reconstitution inflammatory syndrome (IRIS), was suspected in one patient, who had worsening shortly after infusion, but in which MRI did not show contrast enhancement, which was interpreted that IRIS was unlikely.

In our patient a rapid worsening with encephalopathy was observed shortly after pembrolizumab infusion without MRI enhancement. Despite the lack of contrast enhancement on MRI, we are concerned that the progression may have been provoked by the PD1-inhibitor treatment. Although the observed efficacy ofPD-1 inhibitor treatment is promising, cases of PML have been reported after treatment with nivolumab or pembrolizumab, why the use of this treatment should be cautious (36).

Conclusion

JCV-GCN may complicate ALPS and may progress to PML. In JCV-GCN, wild-type and JCV-VP-1 can co-exist in CSF. Quantification and sequencing of JCV in CSF is helpful to characterize and monitor disease and treatment. Progression of disease may be associated with development of T-cell exhaustion, but the benefit PD-1 inhibitor treatment is uncertain.

Abbreviations

JCV: JC-virus

JCV-GCN: JC-virus associated granular cerebellar neuronopathy (JCV-GCN)

PML: Progressive Multifocal Leucoencephalopathy

ALPS- FAS: Autoimmune Lymphoproliferative Syndrome with FAS mutation.

CVID: Common Variable Immunodeficiency (CVID)

AIHA: Autoimmune Hemolytic Anemia

DNT: Double negative T cell

HPV: Human papilloma virus

Declarations

Ethics approval and consent to participate:

Consent was obtained from the patient and family. Ethics approval: Not applicable.

Consent for Publication:

Consent was obtained from the parents

Competing interests:

The authors declare that they have no competing interest.

Availability of supporting data:

Not applicable

Funding:

None.

Acknowledgements:

Not applicable

Authors' contributions:

JHL and DK directed the investigations, clinical management, interpreted the results and wrote the primary manuscript. MoR, MaR and AF did virological sequencing and bioinformatic analysis. RLM performed and analyzed exome sequencing. JTB, LPR, HVM and LMRG performed histology and

immunological analysis. FS, RB and PG provided neurological, neuroradiological analysis and interpretation. All authors contributed to the final manuscript.

References

1. Du Pasquier RA, Corey S, Margolin DH, Williams K, Pfister LA, De Girolami U, et al. Productive infection of cerebellar granule cell neurons by JC virus in an HIV+ individual. Neurology. 2003;61(6):775–82.
2. Koralnik IJ, Wüthrich C, Dang X, Rottnek M, Gurtman A, Simpson D, et al. JC virus granule cell neuronopathy: A novel clinical syndrome distinct from progressive multifocal leukoencephalopathy. Ann Neurol. 2005;57(4):576–80.
3. Miskin DP, Koralnik IJ. Novel syndromes associated with JC virus infection of neurons and meningeal cells. Curr Opin Neurol [Internet]. 2015;28(3):1. Available from: http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00019052-900000000-99436
4. Rieux-Laucat F, Magérus-Chatinet A, Neven B. The Autoimmune Lymphoproliferative Syndrome with Defective FAS or FAS-Ligand Functions. J Clin Immunol [Internet]. 2018;2:558–68. Available from: http://link.springer.com/10.1007/s10875-018-0523-x
5. Bride K, Teachey D. Autoimmune lymphoproliferative syndrome: more than a FAScinating disease. F1000Research [Internet]. 2017;6(0):1928. Available from: https://f1000research.com/articles/6-1928/v1
6. Price S, Shaw PA, Seitz A, Joshi G, Davis J, Niemela JE, et al. Natural history of autoimmune lymphoproliferative syndrome associated with FAS gene mutations. Blood. 2014;123(13):1989–99.
7. Andersen P, Permin H, Andersen V, Schejbel L, Garred P, Svejgaard A, et al. Deficiency of somatic hypermutation of the antibody light chain is associated with increased frequency of severe respiratory tract infection in common variable immunodeficiency. Blood. 2005;105(2):511–7.
8. Ambati J, Wynne KB, Angerame MC, Robinson MR. Anterior uveitis associated with intravenous cidofovir use in patients with cytomegalovirus retinitis. Br J Ophthalmol [Internet]. 1999;83(10):1153–8. Available from: http://www.ncbi.nlm.nih.gov/pubmed/10502577
9. Chan JFW, Ma MKM, Chan GSW, Chan GCW, Choi GKY, Chan KH, et al. Rapid reduction of viruria and stabilization of allograft function by fusidic acid in a renal transplant recipient with JC virus-associated nephropathy. Infection. 2015;43(5):577–81.
10. Brickelmaier M, Lugovskoy A, Kartikeyan R, Reviriego-Mendoza MM, Allaire N, Simon K, et al. Identification and characterization of mefloquine efficacy against JC virus in vitro. Antimicrob Agents Chemother. 2009;53(5):1840–9.
11. Mindermann T, Zimmerli W, Rajacic Z, Gratzl O. Penetration of fusidic acid into human brain tissue and cerebrospinal fluid. Acta Neurochir (Wien). 1993;121(1–2):12–4.

12. Hedberg A, Hårdemark HG, Olsson-Liljequist B, Sjölin J. Penetration of fusidic acid and rifampicin into cerebrospinal fluid in low-grade inflammatory meningitis caused by Staphylococcus epidermidis. Clin Microbiol Infect. 2004;10(8):765–8.
13. de Louvois J, Gortvai P, Hurley R. Antibiotic treatment of abscesses of the central nervous system. Br Med J. 1977;2(6093):985–7.
14. Tan CS, Bord E, Broge Jr TA, Glotzbecker B, Mills H, Gheuens S, et al. Increased Program Cell Death - 1 (PD-1) Expression on T Lymphocytes of Patients with Progressive Multifocal Leukoencephalopathy (PML). J Acquir Immunde Defic Syndr. 2012;60(3):244–8.
15. Ryschkewitsch CF, Jensen PN, Major EO. Multiplex qPCR assay for ultra sensitive detection of JCV DNA with simultaneous identification of genotypes that discriminates non-virulent from virulent variants. J Clin Virol [Internet]. 2013;57(3):243–8. Available from: http://dx.doi.org/10.1016/j.jcv.2013.03.009
16. Dang X, Koralnik IJ. A granule cell neuron-associated JC virus variant has a unique deletion in the VP1 gene. J Gen Virol. 2006;87(9):2533–7.
17. Dang X, Koralnik IJ. A granule cell neuron-associated JC virus variant has a unique deletion in the VP1 gene. J Gen Virol. 2006;87(9):2533–7.
18. Zerbe CS, Marciano BE, Katial RK, Santos CB, Adamo N, Hsu AP, et al. Progressive Multifocal Leukoencephalopathy in Primary Immune Deficiencies: Stat1 Gain of Function and Review of the Literature. Clin Infect Dis [Internet]. 2016;62(8):986–94. Available from: http://www.ncbi.nlm.nih.gov/pubmed/26743090
19. Hadjadj J, Hermine O, Suarez F, Guffroy A, Delavaud C, Taieb G, et al. Progressive Multifocal Leukoencephalopathy in Primary Immunodeficiencies. J Clin Immunol. 2018;55–64.
20. McLean-Tooke A, Phatouros CC, Chidlow G, Smith DW, Silbert P. Granule Cell Neuronopathy in a Patient with Common Variable Immunodeficiency. J Clin Immunol. 2019;39(3):267–9.
21. Zerbe CS, Marciano BE, Katial RK, Santos CB, Adamo N, Hsu AP, et al. Progressive Multifocal Leukoencephalopathy in Primary Immune Deficiencies: Stat1 Gain of Function and Review of the Literature. Clin Infect Dis. 2016;62(8):986–94.
22. Tan CS, Broge TA, Seung E, Vrbanac V, Viscidi R, Gordon J, et al. Detection of JC Virus-Specific Immune Responses in a Novel Humanized Mouse Model. PLoS One. 2013;8(5).
23. Abraham RS, Recher M, Giliani S, Walter JE, Lee YN, Frugoni F, et al. Adult-onset manifestation of idiopathic T-cell lymphopenia due to a heterozygous RAG1 mutation. J Allergy Clin Immunol [Internet]. 2013 May;131(5):1421–3. Available from: http://www.ncbi.nlm.nih.gov/pubmed/23122631
24. Cortese I, Muranski P, Enose-Akahata Y, Ha S-K, Smith B, Monaco M, et al. Pembrolizumab Treatment for Progressive Multifocal Leukoencephalopathy. N Engl J Med. 2019;380(17):1597–605.
25. Harypursat V, Zhou Y, Tang S, Chen Y. JC Polyomavirus, progressive multifocal leukoencephalopathy and immune reconstitution inflammatory syndrome: A review. AIDS Res Ther [Internet]. 2020;17(1):1–11. Available from: https://doi.org/10.1186/s12981-020-00293-0

26. De Luca A, Ammassari A, Pezzotti P, Cinque P, Gasnault J, Berenguer J, et al. Cidofovir in addition to antiretroviral treatment is not effective for AIDS-associated progressive multifocal leukoencephalopathy: A multicohort analysis. Aids. 2008;22(14):1759–67.
27. Jiang Z, Cohen J, Marshall LJ, Major EO. Hexadecyloxypropyl-cidofovir (CMX001) suppresses JC virus replication in human fetal brain SVG cell cultures. Antimicrob Agents Chemother [Internet]. 2010;54(11):4723–32. Available from: http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=2976159&tool=pmcentrez&rendertype=abstract
28. Ellrichmann G, Behrendt V, Grunwald C, Schlottmann R, Lukas C, Gold R. Cidofovir for treatment of progressive multifocal leukoencephalopathy in a newly diagnosed sarcoidosis patient - A valid therapeutic option? J Neurol Sci. 2016;362:341–3.
29. Yagi T, Hattori H, Ohira M, Nakamichi K, Takayama-Ito M, Saijo M, et al. Progressive multifocal leukoencephalopathy developed in incomplete Heerfordt syndrome, a rare manifestation of sarcoidosis, without steroid therapy responding to cidofovir. Clin Neurol Neurosurg. 2010 Feb;112(2):153–6.
30. Eckert S, Weinstock-Guttman B, Kolb C, Hojnacki D. Treatment of natalizumab-induced PML with cidofovir or CMX001 (brincidofovir) and mirtazapine (P5.380). Neurology [Internet]. 2018;90(15 Supplement):258. Available from: http://n.neurology.org/content/90/15_Supplement/P5.380.abstract
31. Naess H, Glad S, Storstein A, Rinaldo CH, Mørk SJ, Myhr K, et al. Progressive multifocal leucoencephalopathy in an immunocompetent patient with favourable outcome. A case report. BMC Neurol [Internet]. 2010 May 18;10:32. Available from: http://www.biomedcentral.com/1471-2377/10/32
32. Hoang E, Bartlett NL, Goyal MS, Schmidt RE, Clifford DB. Progressive multifocal leukoencephalopathy treated with nivolumab. J Neurovirol. 2019;284–7.
33. Audemard-Verger A, Gasnault J, Faisant M, Besse MC, Martin-Silva N, Berra M, et al. Sustained Response and Rationale of Programmed Cell Death-1-Targeting for Progressive Multifocal Leukoencephalopathy. Open Forum Infect Dis. 2019;6(10):1–4.
34. Walter O, Treiner E, Bonneville F, Mengelle C, Vergez F, Lerebours F, et al. Treatment of progressive multifocal leukoencephalopathy with nivolumab. N Engl J Med. 2019;380(17):1674–6.
35. Rauer S, Marks R, Urbach H, Warnatz K, Nath A, Holland S, et al. Treatment of Progressive Multifocal Leukoencephalopathy with Pembrolizumab. N Engl J Med [Internet]. 2019 Apr 25;380(17):1676–7. Available from: http://www.nejm.org/doi/10.1056/NEJMc1817193
36. Focosi D, Tuccori M, Maggi F. Checkpoint inhibitors and progressive multifocal leukoencephalopathy: friends of foes? Ann Transl Med. 2019;7(S8):S298–S298.

Figures

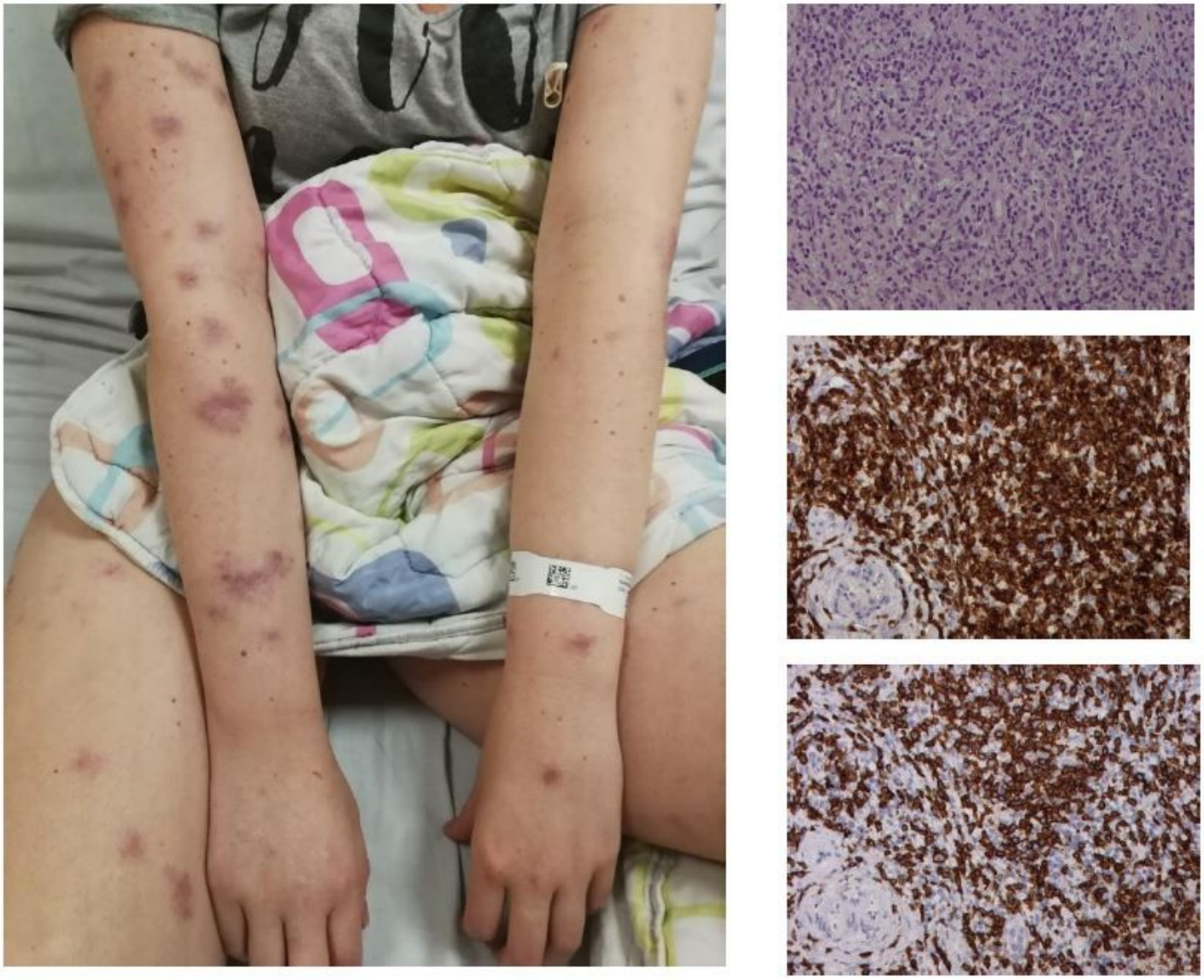


Figure 1

Left: Nodular skin lesions. Right-top: Skin biopsy, demonstrating dense small and medium size CD3-positive lymphohistiocytic infiltration (middle) with CD8 predominance (bottom).

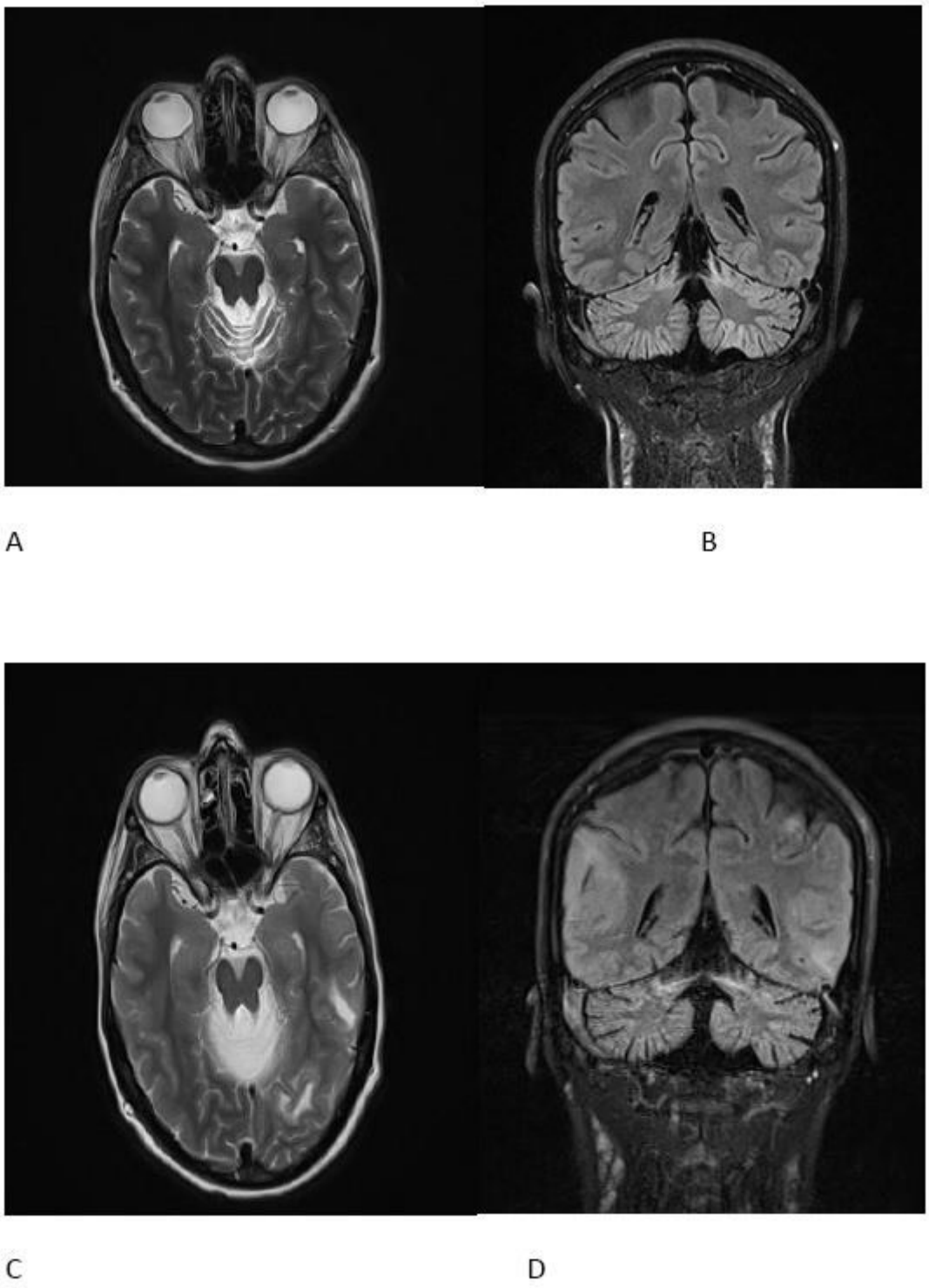


Figure 2

MRI findings Legend for figure 2: A and B: Severe atrophy of cerebellar vermis at diagnosis. C and D: Progression to PML.

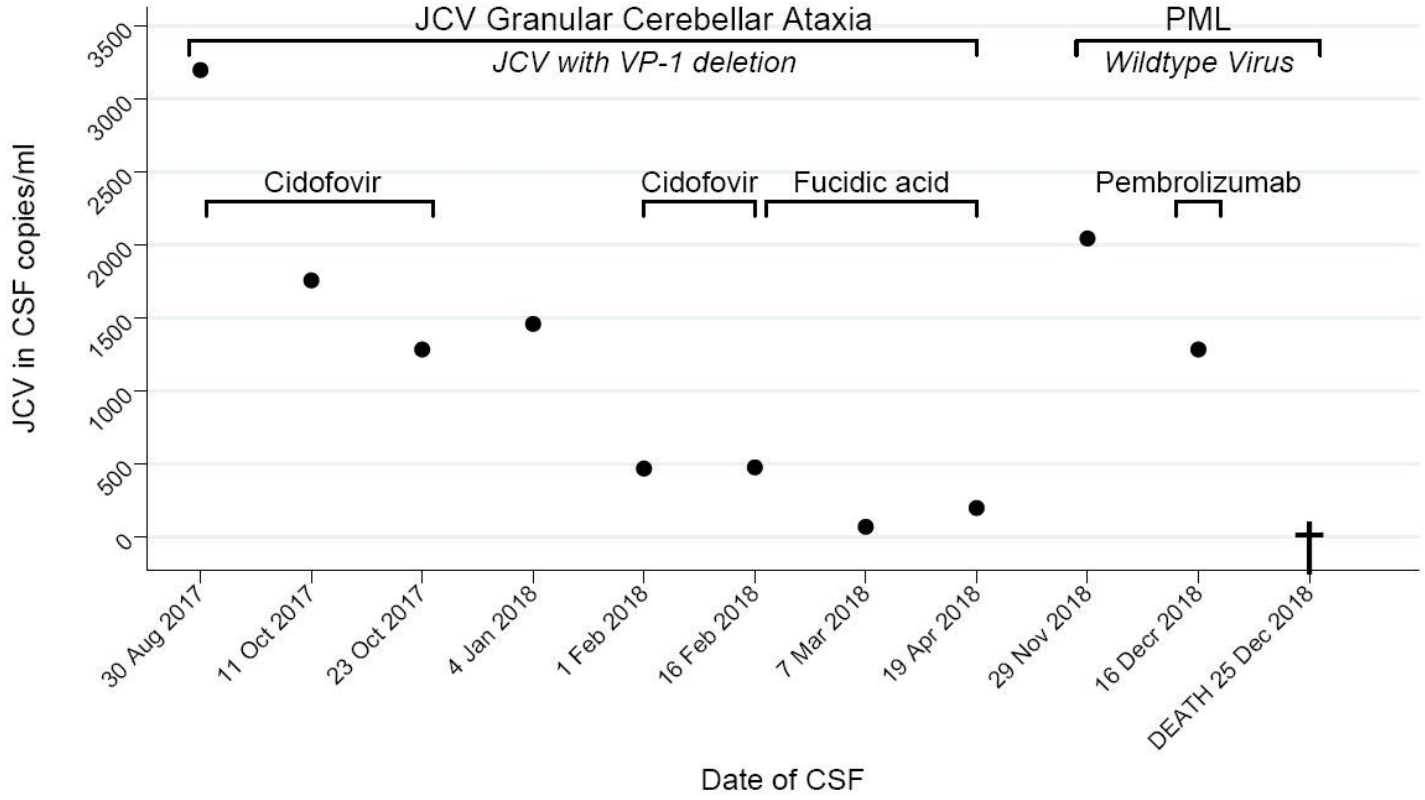


Figure 3

Timeline of JCV-CSF findings and treatment from diagnosis of JCV-GN to PML and death

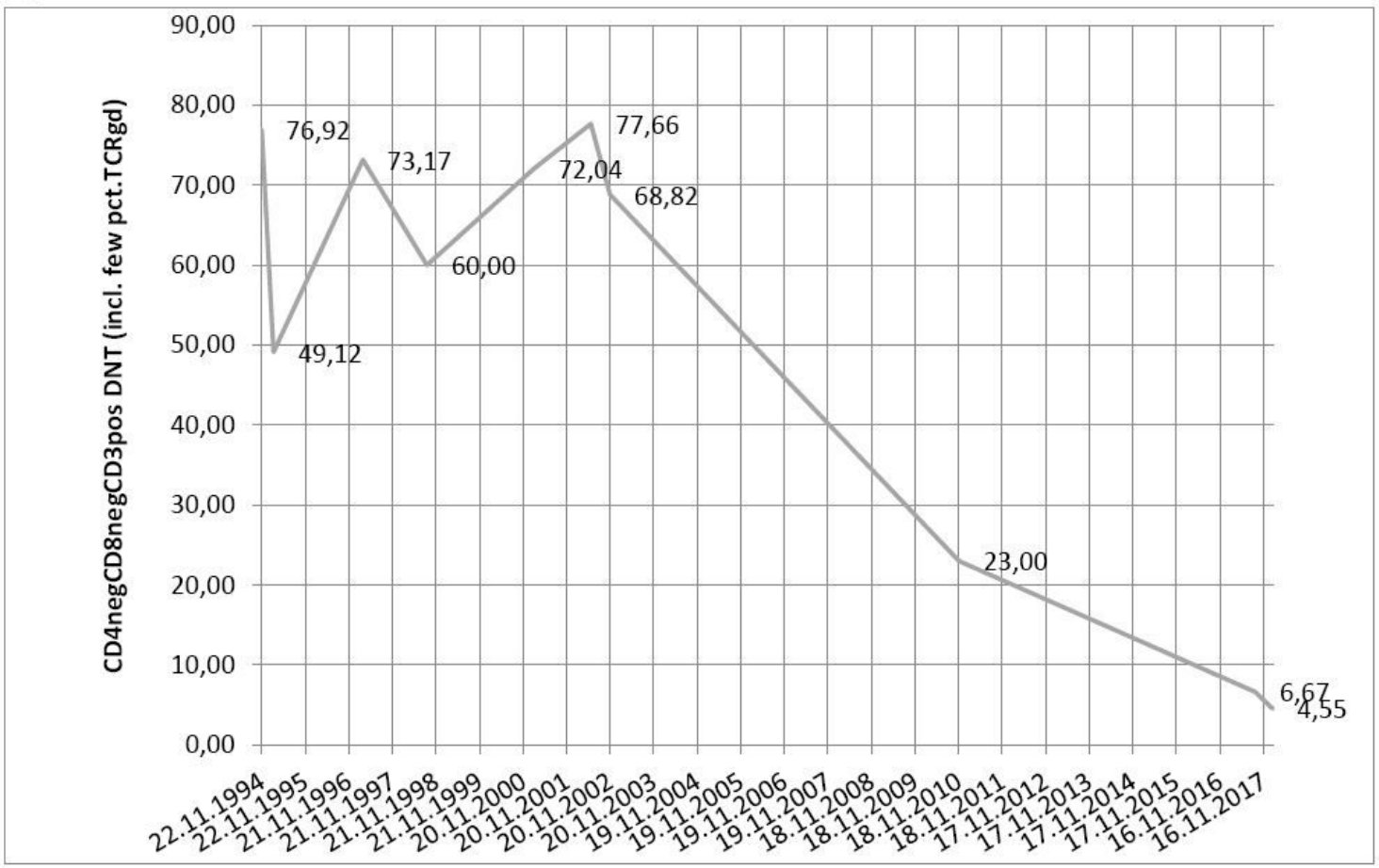


Figure 4

Changes in Double Negative T-cells (DNT) over time.

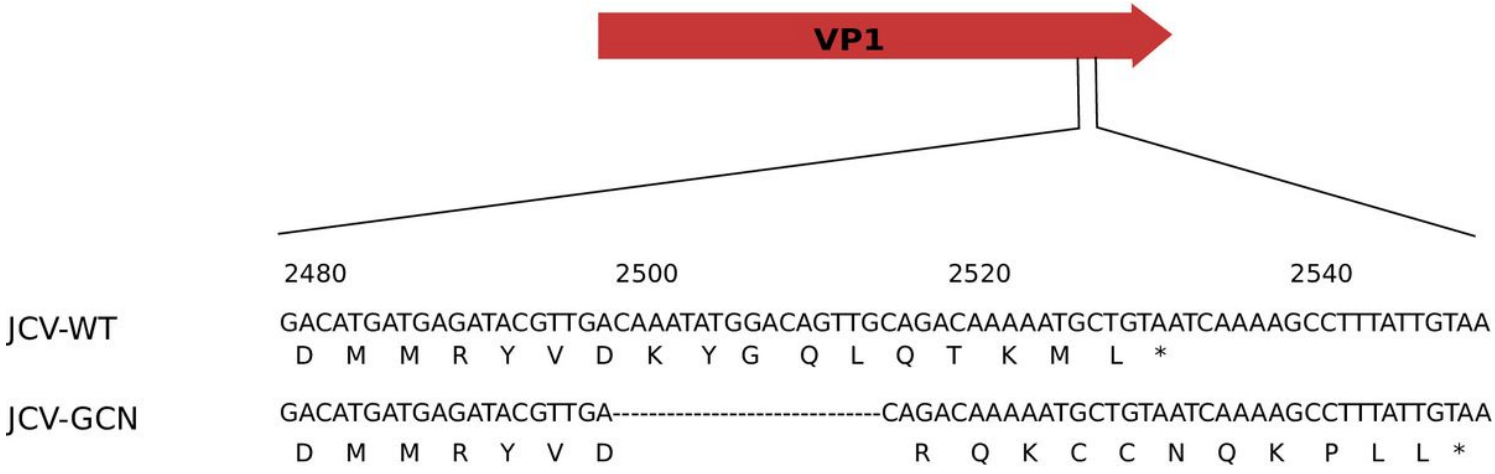


Figure 5

Sequences of JCV with VP1 deletion and wildtype