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A case of progressive multifocal leukoencephalopathy and idiopathic CD4+ lymphocytopenia

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Sir,
We present the case of a patient with progressive multifocal leukoencephalopathy (PML), caused by the human polyoma virus JC, who was found to have a CD4+ count of 87 cells/mm³ and was subsequently diagnosed with idiopathic CD4+ lymphocytopenia (ICL). To our knowledge, this is the first reported case on the use of multiple agents targeted against both PML and ICL.

A patient presented at an outside hospital with progressive right-sided weakness, numbness, mouth droop and speech loss. At that time, the patient was diagnosed with an ischaemic cerebrovascular accident and was started on appropriate therapy. Despite physical therapy, the patient continued to deteriorate and was re-evaluated after 2 months. Magnetic resonance imaging (MRI) at that time revealed progression of stroke

or possible neoplasm, and extensive workup showed no evidence of vascular abnormality or CNS vasculitis. The patient had no risk factors for HIV infection and past medical history was unremarkable. The patient was transferred to our institution for further evaluation.

Upon admission, the patient presented with slurred speech, difficulty verbalizing their thoughts and right-sided weakness. Laboratory results included a normal white blood cell count, with normal neutrophil and slightly depressed lymphocyte counts. MRI revealed multiple white matter lesions throughout the brain, consistent with a demyelinating process. A brain biopsy confirmed characteristic findings of PML, with enlarged oligodendroglial nuclei and intranuclear ground glass-type inclusions. *In situ* hybridization for JC viral genome sequences was positive and the JC viral load was reported as 3600 copies/mL.

Because of the PML diagnosis, HIV screening, T cell subset cell count and immunoglobulin tests were carried out. Serological tests by ELISA and PCR analysis were negative for HIV-1, HIV-2 and human T-lymphotropic virus-1 and -2, and immunoglobulin studies were normal (IgG total 974 mg/dL, IgG1 501 mg/dL, IgG2 217 mg/dL, IgG3 64 mg/dL, IgG4 4 mg/dL, IgA 350 mg/dL and IgM 210 mg/dL). Initial T cell counts were markedly decreased at 87 and 111 cells/mm³. Based upon these results, a diagnosis of PML with ICL was made and the challenge of creating an appropriate treatment regimen began.

After a discussion of potential options and a review of published literature, as described in the accompanying review article,¹ therapy was initiated with three main goals: (i) to decrease JC virus levels; (ii) to increase CD4+ cell counts; and (iii) to prevent other opportunistic infections. Because the available options for the treatment of PML are limited and published data are based on case reports, it was decided to provide a combination of agents shown to be active against JC virus. The

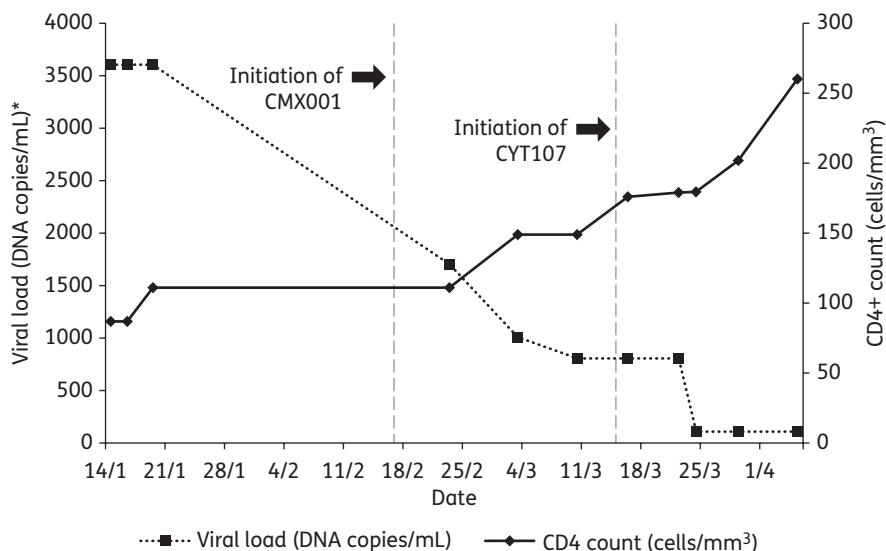


Figure 1. Patient trend in viral load and CD4+ count. *Assay unable to detect viral load below a lower limit of 100 DNA copies/mL.

patient was started on cidofovir [5 mg/kg intravenous (iv) ×2 weeks], risperidone (2 mg orally every 12 h) and mefloquine (250 mg orally ×3 days, then weekly). An investigational oral agent for the treatment of PML, CMX001, was given to the patient after the initial 2 weeks of iv cidofovir. The patient also received an investigational interleukin-7 (CYT107) to increase their CD4+ cell counts. Initiation of this therapy was delayed until viral loads decreased, in order to avoid immune reconstitution syndrome. Finally, the patient was given appropriate prophylaxis with dapsone (100 mg orally daily), according to CDC recommendations for a CD4+ count of <200 cells/mm³.

Four weeks after the initiation of therapy for JC virus with risperidone, iv cidofovir and mefloquine, the patient's serum viral load was 3456 copies/mL. The patient's neurological function was declining, as their left hand started becoming weaker and they had difficulty swallowing and speaking. Repeat MRI showed a new area of dysfunction in the right portion of the brain that correlated with weakness in the left hand and persistent presence of demyelination in multiple areas of the brain. It is important to note that, at this point, iv cidofovir was discontinued after two doses. In addition, we noticed a drop in the patient's haemoglobin and, with a suspicion for haemolytic anaemia, both mefloquine and dapsone were discontinued. CMX001 was then initiated and, 1 week later, the serum viral load had decreased to 1700 copies/mL. Subsequent values were 800, 100 and 100 copies/mL at 3, 5 and 7 weeks after CMX001 initiation, respectively. Changes in CD4+ counts and viral loads over time are shown in Figure 1. By day 7 of

CMX001 treatment, neurological function stabilized and the patient has not had any further decline since that time. A recent swallowing study showed improvement and our patient is now tolerating a pureed diet.

This was the first case report to demonstrate the use of multiple agents, including investigational medications, as a possible therapeutic strategy in the treatment of PML with ICL. The patient's clinical symptoms are slowly improving and the reduction in viral load over 8 weeks of therapy is promising, but long-term evaluation will be necessary. In addition, further controlled studies are important to determine whether these approaches are effective against the two rare and debilitating diseases.

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Transparency declarations

None to declare.

References

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