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Effectiveness of Immune Checkpoint Inhibitors in Transplant Recipients with Progressive Multifocal Leukoencephalopathy

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Antibodies against PD1 have been used to treat progressive multifocal leukoencephalopathy (PML), a rare brain disease caused by JC virus. We used these antibodies (nivolumab) to treat PML in 3 kidney transplant recipients. All died within 8 weeks of diagnosis. Hence, nivolumab did not improve PML outcome after solid organ transplantation.

The role of T-cell exhaustion in the development of progressive multifocal leukoencephalopathy (PML), a rare brain disease caused by JC virus, has prompted clinicians to use immune checkpoint inhibitor molecules to treat JC virus–infected patients. Recently, Cortese et al. (*1*) used antibodies against PD1 to treat PML in 8 patients (6 with a history of blood disorders and 2 with HIV infection). They noted improvement or stabilization of symptoms for 5 patients but no benefit for the others.

Since 2017, we have treated PML in 3 kidney transplant recipients with a definitive diagnosis, according to the American Academy of Neurology (https://www.aan.com) consensus, made 5 (range 2–17) years after transplantation. We have compiled clinical and radiologic findings for these patients (Appendix Figures 1–3, https://wwwnc.cdc.gov/EID/article/25/11/19-0705-App1.pdf). Since transplantation, the patients had been receiving mycophenolic acid and steroids with either belatacept (n = 1) or tacrolimus (n = 2). At PML diagnosis, immunosuppressants were immediately withdrawn, and nivolumab (antibodies against PD1) was given at a dose of 3 mg/kg every 15 days (2 injections for 2 patients and 3 injections for 1) (Table). For the patient who had received belatacept, we performed 3 apheresis sessions to remove the drug before nivolumab initiation. All patients died within the first 8 weeks after PML diagnosis because of rapid progression of neurologic symptoms.

Table. Characteristics of 3 patients with PML who received nivolumab, France, 2017*

Patient characteristics	Total lymphocytes; CD4+; CD8+, n/mm^3	Clinical course	Additional therapy	JCV in CSF, log_{10} copies/mL	Loss of kidney function
Patient 1: age 81 y; received transplant 5 y before PML diagnosis; received treatment with Tac, MPA, prednisone	B: 300; 76; 56/LFU: 1,000; 602; 250†	Rapid progression of neurologic disorders despite 2 injections of nivolumab; death from progression of PML 6 wk after diagnosis	Mirtazapine 15 mg/d	B: 3.5/LFU: NA	No
Patient 2: age 77 y; received transplant 2 y before PML diagnosis; received treatment with belatacept, MPA, and prednisone	B: 377; 162; 106/LFU: 444; 117; 210‡	Rapid progression of neurologic disorders despite 3 injections of nivolumab; death from progression of PML 6 wk after diagnosis	Mirtazapine 15 mg/d; γ interferon therapy (100 μg) added 1 day after second and third injections	B: 2.9/LFU: 5	Yes
Patient 3: age 67 y; received transplant 17 y before PML diagnosis; received treatment with Tac, MPA, prednisone	B: 487; 287; 67/LFU: 2,076; 1,183; 477§	Rapid neurologic degradation despite 2 injections of nivolumab; death from progression of PML 4 wk after diagnosis	Mirtazapine 15 mg/d	B: 2.9/LFU: NA	No

*B, baseline; CSF, cerebrospinal fluid; JCV, JC virus; LFU, last follow-up; MPA, mycophenolic acid; NA, not available, PML, progressive multifocal leukoencephalopathy; Tac, tacrolimus.
†LFU for patient 1 was 1 wk after the second injection of nivolumab.
‡LFU for patient 2 was 4 d after the third injection of nivolumab.
§LFU for patient 3 was 1 wk after the second injection of nivolumab.

Magnetic resonance imaging was performed before each injection and a few days before death, but images showed no signs of immune reconstitution inflammatory syndrome. Conversely, images did show progression of PML features. As expected, the percentage of T cells expressing PD1, which was assessed for 2 patients, dramatically decreased after receipt of nivolumab (Appendix Figure 4), whereas other inhibitory receptors tested (2b4 and CD160) remained stable or increased. In addition, functional analysis showed a reduction of cytokine production by CD4+ and CD8+ T cells and an improvement of cytotoxic ability, a phenotype compatible with more terminally differentiated exhausted cells, which are less likely to respond to anti-PD1 immune checkpoint inhibitor (*2*).

Research has suggested that PML could occur at any time after transplantation (*3*), even several years after engraftment, which was the case for the 3 patients reported here. As opposed to the results reported by Cortese et al. (*1*), the outcomes for the 3 patients we report, who received nivolumab, was very bad and in line with the PML outcomes usually reported after solid-organ transplant patients (i.e., median survival time <6 months) (*3*). The difference between the patients reported by Cortese et al. and the patients that we report is probably use of immunosuppressive agents (calcineurin inhibitors or costimulation blockers) that can lead to persistent T-cell dysfunction, despite withdrawal of these treatments, resulting in refractory T-cell dysfunction after use of anti-PD1 blockers, as reported in ex vivo experiments (*4*). This hypothesis is supported by the absence of kidney rejection in 2 of the 3 patients. Of note, all 5 patients reported by Cortese et al. (*1*) for whom anti-PD1 blockers were efficient were not receiving immunosuppressive therapy at PML diagnosis.

Moreover, the 3 patients reported here had profound lymphopenia at diagnosis, which for 2 patients did not improve after receipt of nivolumab (Table). Although there is no established relationship between the severity of lymphopenia and the response to anti-PD1, the 3 patients with unfavorable outcomes reported by Cortese et al. (*1*) also had severe lymphopenia. This finding suggests that immunotherapies can be ineffective in patients with severe lymphopenia. The use of ex vivo expanded, BK virus–specific T cells (*5*) should be tested in this setting. For the kidney transplant patients with PML reported here, use of nivolumab, associated with immunosuppressive therapy withdrawal, did not restore efficient immune response and did not improve the outcomes.

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Endemicity of Yaws and Seroprevalence of *Treponema pallidum* Antibodies in Nonhuman Primates, Kenya

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Human yaws has historically been endemic to Kenya, but current epidemiologic data are lacking. We report seroprevalence for *Treponema pallidum* antibodies in olive baboons (*Papio anubis*) and vervet monkeys (*Chlorocebus pygerythrus*) in Laikipia County, Kenya. Our results suggest endemicity of the yaws bacterium in monkeys, posing a possible zoonotic threat to humans.

Yaws is a disease caused by the bacterium *Treponema pallidum* subsp. *pertenue*, which is believed to be an exclusively human pathogen (*1*). However, this bacterium has recently been identified in African nonhuman primates (NHPs) (*2*), raising concerns about a possible zoonotic reservoir for human infection. Kenya is 1 of 76 countries that the World Health Organization categorizes as previously endemic for yaws, but no current data support its presence or absence (http://apps.who.int/gho/data/node.main.NTDYAWSEND). However, sustainable yaws eradication will rely on information about transmission dynamics and potential links between human and NHP *T. pallidum* strains (*3*).

In the early 1960s, Fribourg-Blanc and Mollaret tested 150 serum samples from wild-caught baboons (*Papio* sp.) from Guinea and Kenya (*4*). Although 72 (65%) of 111 serum samples from Guinea were positive for *T. pallidum* antibodies, none of the samples from Kenya were positive. In subsequent years, an additional 276 serum samples from baboons in Kenya supported the absence of *T. pallidum* infection. However, a more recent study of baboon samples collected during 1977–1994 in Kenya reported serologic evidence of *T. pallidum* infection in Nanyuki, Laikipia County (prevalence 57.5%) (*5*). For our study, we hypothesized that 39 years after the first samples were positive for antibodies against *T. pallidum* in Nanyuki (*5*), infection is still present in the NHP population.

All animal protocols were approved by the Kenya Wildlife Service (permit #4004), the Institute of Primate Research Scientific and Ethics Review Committee, and the Smithsonian Institution Animal Use and Care Committee. In October 2016, we sampled 65 olive baboons (*Papio anubis*) and 2 vervet monkeys (*Chlorocebus pygerythrus*) at sites surrounding the Mpala Research Centre in Laikipia County, Kenya. We performed a preliminary serologic screening by using the immunochromatographic Dual Path Platform (DPP) HIV-Syphilis Assay (Chembio Diagnostic Systems, Inc., http://chembio.com) according to the manufacturer guidelines. This syphilis (*T. pallidum*) assay is a useful screening tool because antibodies against *Treponema* subspecies are cross-reactive (*6*). We tested 67 samples with the DPP assay; 49 were positive and 18 negative.

However, because this test is not certified for use with NHPs, we subsequently confirmed results by using the *T. pallidum* Particle Agglutination Assay (TPPA) (SERODIA TPPA, https://www.fujirebio-us.com), which has been validated for use in baboons (*7*). Of the 52 samples tested with the TPPA assay, there were 33 positive, 6 negative, and 13 inconclusive results. Inconclusive TPPA results indicate nonspecific antibodies reacting with nonsensitized particles. Because of limited sample material, we were unable to perform repeated testing with a preabsorption step to remove all nonspecific binding antibodies (as described in the assay manual) and therefore excluded the inconclusive TPPA results from our analysis.