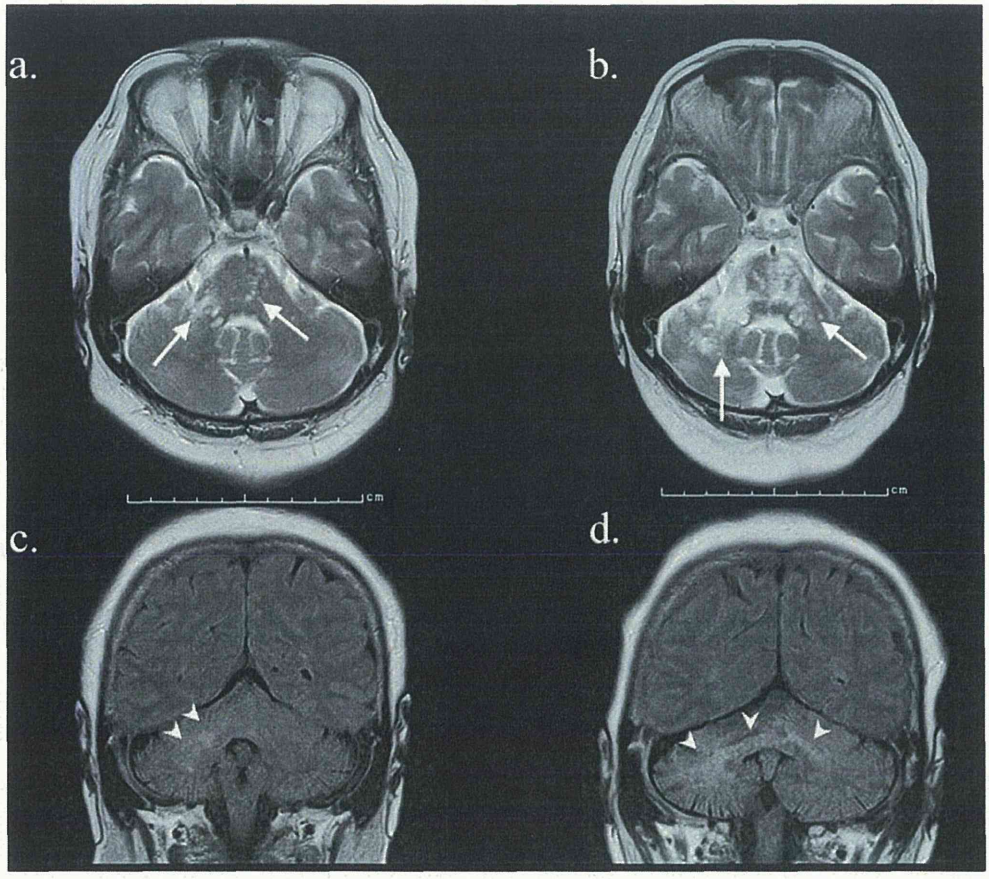

Fig. 1. Brain MRI showing white matter involvement by lesions in the pons and right pedunculus cerebellaris medius in T2-weighted axial (white arrows in a) and FLAIR coronal (white arrowheads in c) images. After 3 months, abnormal white matter involvement was expanded in both T2-weighted axial (white arrows in b) and FLAIR coronal (white arrowheads in d) images. These lesions were not enhanced after administration of contrast material (image not shown).

of albumin and IgG. Flow cytometric analyses of lymphocytes revealed increases in $CD8^+$ T cells and $CD8^+CD11a^+$ T cells in the CSF (48.9% and 41.1%, respectively), in contrast to normal levels of those populations in peripheral blood (36.4% and 26.4%, respectively). Serum titers for anti-EBV-VCA IgG and anti-EBV-EADR IgG antibodies were ×320 and ×160, respectively, whereas those antibodies were undetected in the CSF. Brain MRI showed white matter lesions in the pons and right pedunculus cerebellaris medius in T_2-weighted and FLAIR images (Fig. 1a and c), while gadolinium enhancement was negative. In whole-body ^{18}F-fluorodeoxy glucose (FDG) PET-CT scanning, high uptake was not detected.

At a 3-month follow-up examination, cerebellar dysfunction had worsened and lesions shown by MRI were expanded to the right cerebellar hemisphere (Fig. 1b and d). At that time, analyses of CSF samples using ultrasensitive quantitative real-time PCR were performed for detection of JCV-DNA, including the large T and VP1 genes, with negative results. Without a definite diagnosis of PML, MMF was discontinued, and treatments with short-term intravenous corticosteroids and cytarabine were begun. However, the patient died 8 months later due to respiratory failure. An autopsy revealed the presence of so-called bizarre astrocytes and oligodendrocytes with enlarged nuclei, as well as anti-JCV antibody-positive oligodendrocytes associated with demyelination, along with atrophy and depletion of granular and Purkinje cells in the cerebellum. Furthermore, extensive microscopic demyelinating lesions were detected in cerebral white matter. These findings were compatible with those of PML previously reported (Fig. 2).

3. Discussion

We treated a patient who developed PML 26 years after undergoing kidney transplantation. PML has been reported to occur in patients who receive organ transplantation, because of the necessity of immunosuppressive treatment. The median time of onset of PML following transplantation in such reported cases is 17 months, with 71% developing PML within 24 months [1]. In contrast, that study also noted a trend of delayed development of the condition in patients who underwent renal transplantation, with a median onset time of 30 months, which was speculated to be due to the amount of immunosuppressants given, as that used for renal transplant patients is lower as compared to other organ transplant patients. There was an extremely long interval between renal transplantation and development of PML in our patient. We considered that an increase in $CD8^+CD11a^+$ T cells in the CSF might have affected the natural course, as this population includes cytotoxic T cells that play an important role in eliminating viruses from infected CNS tissues in HTLV-I-associated myelopathy [2]. On the other hand, an increase in $CD8^+$ T cells in peripheral blood and infiltration of $CD8^+$ T cells in brain white matter have been found in patients with PML who are also affected by immune reconstitution inflammatory syndrome (PML-IRIS). However, it is unlikely that our patient developed PML-IRIS, since she did not respond to intravenous corticosteroids.

MMF is given to more than 75% of renal transplant recipients in the United States, with the incidence of PML in those users reported to be 14.4 cases/100,000 person-years, while that in

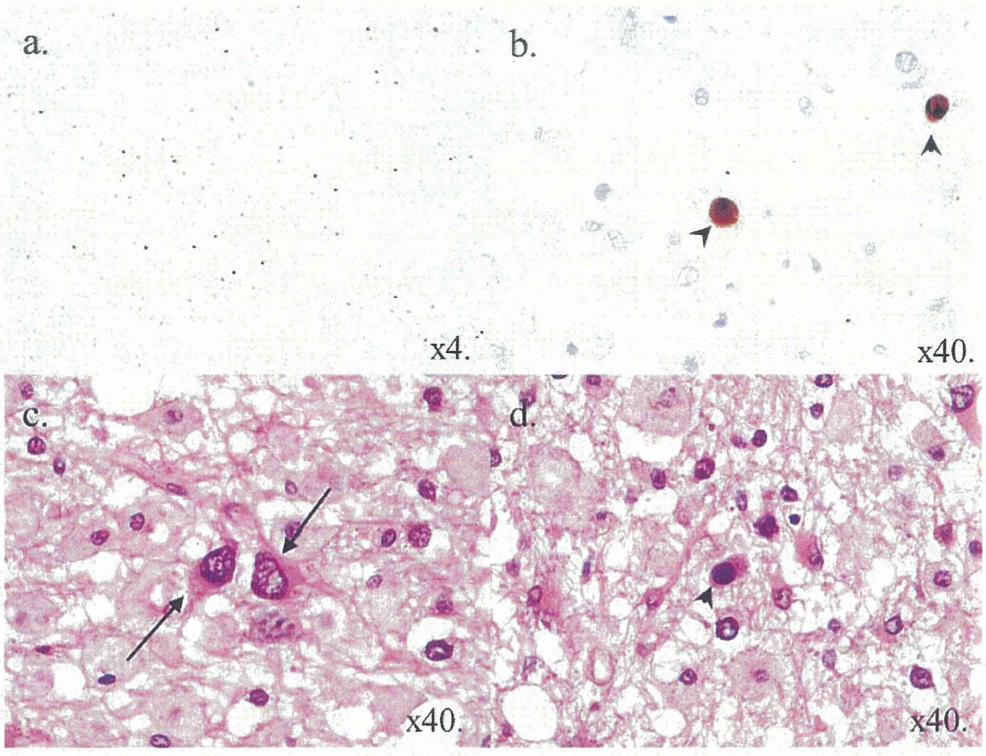

Fig. 2. An autopsy was performed 3 h after death. Immunostaining identified anti-JCV antibody positive deposits in the nuclei of oligodendrocytes in cerebellum white matter (a, black arrowheads in b). Hematoxylin–eosin staining revealed bizarre-looking reactive astrocytes (black arrows in c) and oligodendrocytes with enlarged nuclei, which were filled with homogeneous amphophilic material (black arrowhead in d).

non-MMF users was found to be 0 ($p = 0.11$) [3]. Although there are no significant differences reported between MMF users and non-users, our patient developed PML relatively early after changing to a regimen containing MMF. Similar findings have been reported in patients who underwent renal transplantation [4] and with systemic lupus erythematosus [5]. In those, MMF was discontinued and the patients survived. Since the risk of developing PML in MMF users has not been fully clarified, careful follow-up is necessary when prescribing MMF for patients who have undergone renal transplantation.

4. Conclusion

We reported a rare case of PML that developed 26 years after renal transplantation. PML should be included in a differential diagnosis of transplanted patients, even when new CNS symptoms appear decades later.

Disclosure statement

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