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Title Page

A fatal case of cytomegalovirus ventriculoencephalitis in a mycosis fungoides patient who received multiple umbilical cord blood cell transplantations

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Abstract:

Cytomegalovirus (CMV) infection is latent in the majority of adult humans. The reactivation of CMV causes pneumonia and gastrointestinal disease in severely immunosuppressed patients, who consequently suffer very high mortality due to CMV central nervous system disease. We report here a case involving a 28-year-old female patient with mycosis fungoides who underwent umbilical cord blood transplantation three times and developed CMV ventriculoencephalitis. The patient's CMV viremia was successfully preempted with ganciclovir (GCV) as indicated by undetectable CMV antigenemia, but despite this successful treatment, the patient developed CMV ventriculoencephalitis. Foscarnet (FCV) therapy led to a temporary recovery, after which CMV ventriculoencephalitis recurred and the patient died after receiving combination GCV and FCV therapy. Autopsy samples revealed CMV ventriculoencephalitis, as indicated by numerous inclusion-bearing cells (Owl's eye). It is likely that this patient harbored a GCV-resistant CMV strain; however, it was not possible to obtain nucleic acids suitable for use in assessing this possibility.

Key words: cytomegalovirus ventriculoencephalitis, ganciclovir resistance, umbilical cord blood transplantation, mycosis fungoides, inclusion-bearing cells

Introduction

Cytomegalovirus (CMV) infection is a significant cause of morbidity and mortality as a consequence of hematopoietic stem cell transplantation (HSCT). Prophylaxis and preemptive therapy contribute toward the prevention of CMV disease. Patients are routinely monitored for CMV antigenemia or viral load, and ganciclovir (GCV), foscarnet (FCV), or cidofovir (CDV) must be administered to high-risk patients once CMV viremia develops. However, the prolonged use of GCV possibly leads to an increase of GCV-resistant strains and bone marrow suppression, which presents a risk for secondary engraftment failure. Moreover, FCV and CDV occasionally cause renal insufficiency. Thus, it is problematic to administer these drugs to HSCT patients. Although CMV encephalitis is rare, it is a severe life-threatening disease caused by CMV. We report here the case of a patient with mycosis fungoides (MF) complicated with CMV ventriculoencephalitis after umbilical cord blood transplantation (CBT).

Case report

A 28-year-old Japanese female presented with erythematous patches on her forehead, and these patches along with plaques and tumors gradually spread to her trunk and extremities. The patient was diagnosed with MF (pT2N1M0B0; clinical stage IIA) by skin biopsy. Histopathology showed intraepidermal collections of atypical cells (Pautrier's microabscess). The patient was treated with psoralen–ultraviolet A light and topical steroids. The erythematous patches and tumors became less severe and widespread, but she had swelling of her inguinal lymph nodes and multiple lung tumors appeared (pT3N1M1B0; clinical Stage IV B). The patient received 6 cycles of systemic chemotherapy comprising adriamycin, cyclophosphamide (CY), vincristine (VCR), and prednisolone (PSL), otherwise referred to as CHOP therapy. This provided a partial response, however, electron beam irradiation aggravated. Therefore, we considered that the disease was refractory to chemotherapy and radiotherapy.

Hence, we considered allogeneic HSCT to be an appropriate treatment for her. Because we could not identify a human leucocyte antigen (HLA)-matched related or unrelated donor, umbilical cord blood was chosen as a graft source. Two cycles of thiarubicin, CY, VCR, and PSL (THP-COP) provided a partial response of disease before CBT. CBT (3.71×10^7 cells/kg, HLA allele 3 loci mismatch, female donor) was performed after administering a myeloablative conditioning regimen [CY and total body irradiation

(TBI), CY at 50 mg/kg on day -3 and -2, and TBI at 12 Gy/6 fractions on day -7, -6, and -4]. Levofloxacin (500 mg/day), micafungin (100 mg/day), and acyclovir (200 mg/day) were administered for prophylaxis of bacterial, fungal, and viral infections, respectively. Intravenous (i.v.) immunoglobulin (Ig; 5,000 mg every 2 weeks) was routinely administered to prevent infections. Graft-versus-host disease (GVHD) prophylaxis comprised tacrolimus (0.2 mg/kg/day from day -1) and short-term methotrexate (15 mg/day, day 1 and 10 mg/day, days 3 and 6). Twenty-eight days after CBT, engraftment failure was diagnosed, and a second CBT (2.06×10^7 cells/kg, HLA allele 4 loci mismatch, male donor) was performed after administering fludarabine (Flu), busulfan (Bu), and total lymphoid irradiation (TLI) (Flu at 25 mg/m^2 , starting on day -7 for 6 days; Bu at 4 mg/kg, starting on day -7 for 6 days; and TLI 7.5 Gy, day -1) on day 42 after the first CBT. GVHD prophylaxis consisted of tacrolimus (0.2 mg/kg/day from day 1 before the second CBT) and mycophenolate mofetil (2,000 mg/day from day 1 before the second CBT). Thirty days after the second CBT, engraftment failure was diagnosed again. Forty-eight days after later a third CBT (2.04×10^7 cells/kg, HLA allele 3 loci mismatch, female donor) was performed after administration of Flu, CY, anti-thymocyte globulin (ATG), and methylprednisolone (mPSL) (Flu at 25 mg/m^2 , starting on day -7 for 6 days; CY at 60 mg/kg, on days -7 and -6; ATG at 2.5 mg/kg, starting on day -4 for 4 days; mPSL at 40 mg/day, on day -4 and at 80 mg/day, starting on day -3 for 3 days). GVHD prophylaxis consisted of cyclosporin (3 mg/kg/day starting from day 1 before the third CBT).

The following narrative describes the patient's treatment after the third CBT. Neutrophil recovery was observed on day 22. On day 67, engraftment was confirmed in the bone marrow by chimerism analysis. Skin eruptions and tumors throughout her body were diminished as assessed by positron emission tomography/computed tomography. She remained in complete remission, but CMV antigenemia became detectable (3 positive cells/50,000 cells determined using monoclonal antibody HRP-C7) on day 26 after. Although preemptive therapy was initiated with GCV (5 mg/kg every 12 h), it increased (11 positive cells/50,000 cells) on day 34. The assay became negative following administration of FCV (90 mg/kg every 12 h), but the drug caused renal insufficiency, oliguria, and exacerbation of leg edema. The patient was treated temporarily by the extracorporeal ultrafiltration method and hemodialysis, and the CMV antigenemia remained undetectable. The treatment was changed to administration of GCV (1.25 mg/kg every 12 h) on day 44 and GCV was discontinued on day 104. The patient developed grade I GVHD of

the gastrointestinal tract on day 49, and PSL treatment (1 mg/kg) was initiated, which resulted in diminished GVHD. PSL treatment was tapered off and then discontinued. On day 122, the patient complained of diplopia, and magnetic resonance imaging (MRI) revealed multiple, unfairness hyperintense lesions in the left middle cerebellar peduncle, dorsal medulla oblongata, lateral aperture, and ventral cerebellar hemisphere (Fig. 1). Slight ventriculomegaly was detected by T2-weighted MRI and fluid-attenuated inversion recovery (FLAIR). The apparent diffusion coefficient values determined by diffusion-weighted image MRI were high.

Qualitative PCR analysis of cerebrospinal fluid (CSF) obtained by lumbar puncture detected CMV DNA. Analysis of additional CSF parameters was as follows: 5 mononuclear cells/mm³, glucose = 57 mg/dL (serum glucose = 92 mg/dL), protein = 80 mg/dL, and no culturable bacteria or fungi. All serological and PCR assays of CSF were negative for other pathogens. These findings suggested a diagnosis of CMV ventriculoencephalitis. The absolute CD4 count was 0/mm³. Of note, an ophthalmologist found no signs of CMV retinitis.

Our next approach was to treat the patient was treated with FCV (50 mg/kg every 12 h), but she developed renal insufficiency again. Blood CMV DNA was 130 copies/mL and CMV antigenemia was undetectable. Her neurological status improved, and on day 148, MRI showed that the lesions had diminished. The treatment was then changed to GCV (1.25 mg/kg). On day 157, however, the patient complained of diplopia again. Brain MRI showed lesions with hyperintensity around the left vestibulocochlear nerve in addition to the previous lesions and slight ventriculomegaly detected by T2-weighted MRI. Moreover, by FLAIR, there were hyperintense lesions in the both fornices and lateral ventricles. Lumbar puncture revealed a CSF mononuclear cell count of 162/mm³, a polynuclear cells count of 124/mm³, a glucose level of 57 mg/dL (serum glucose level of 135 mg/dL), and a protein level of 306 mg/dL. CMV DNA was detected in CSF again by qualitative PCR. In contrast, blood CMV antigenemia remained undetectable. The absolute CD4 count was 1/mm³. We concluded that CMV ventriculoencephalitis had recurred, and we treated the patient with GCV (2.5 mg/kg every 12 h) plus FCV (90 mg/kg every 12 h). The patient's neurological condition did not improve, and she died on day 172.

Autopsy revealed edematous and infiltrated inflammatory cells, which were predominantly monocytes, in the ependymal and subependymal white matter of both lateral ventricles, aqueductus cerebri, and the

fourth ventricle. Numerous inclusion-bearing cells were found to be CMV-positive by immunolabeling (Fig. 2).

Discussion

Here, we describe a woman suffering from MF that was refractory to treatment by chemotherapy and radiotherapy. To permit us to initiate more aggressive therapy, we decided to administer HSCT using umbilical cord blood as the source of the graft. It took three difficult rounds of CBT to engraft this patient, and she temporarily achieved complete remission. She then exhibited neurological symptoms, and investigations revealed that they represented CMV ventriculoencephalitis, to which the patient ultimately succumbed.

Clonal expansion of T cells in the skin is the hallmark of cutaneous T-cell lymphoma (CTCL), which presents as topical or generalized skin patches, plaques, or tumors. The 2 most prominent clinical categories (70%–80% of cases) of CTCL are MF and Sézary syndrome. Most cases of MF have an indolent course, and patients with minimal skin disease have an excellent prognosis. MF can progress and especially the more advanced clinical stages of it have a grim prognosis. Both types of MF are treated topically in their early stages and systemically in advanced stages. MF Stage IV patients have a median survival of only 1.5 years or less [1, 2].

Because our patient presented in Stage IIA, her initial treatment was topical, and as described above, required aggressive systemic therapy that required HSCT. Her ultimate demise was established to be caused by CMV, a member of the herpes virus family, which latently infects the majority of adult humans. To our knowledge, the identity of the cells that host latent CMV genomes has not been firmly established. However, evidence indicates that granulocytes and monocytes can silently harbor CMV [3, 4]. The reactivation of CMV causes mononucleosis in otherwise asymptomatic people, as well as pneumonia and gastrointestinal disease in immunosuppressed patients.

The patient described here developed CMV ventriculoencephalitis day 122 after the third round of CBT. Fourteen cases of CMV-induced central nervous system (CNS) disease have been reported (Table 1) [5-17]. Of published cases including ours, the median time of onset of CMV CNS disease was 185 days (range 107–285 days). CMV CNS disease occurs most commonly in patients with severe immunosuppression [18]. Before the onset of CMV CNS disease, all of these cases were diagnosed with

recurrent CMV viremia and had received antiviral therapy. Ventriculoencephalitis is the most common form of CMV CNS disease, but it occurs in <1% of all CMV infections [19], and it is found by autopsy in 33% of acquired immunodeficiency syndrome (AIDS) patients [20], but only rarely in patients who receive HSCT.

The onset of CMV ventriculoencephalitis is characterized by several neurological manifestations, which include apathy, confusion, disorientation, withdrawal, and nystagmus [21]. Interestingly, the patient did not develop CMV retinitis, which predicts an approximately tenfold increased risk of CMV encephalitis in AIDS patients [22]. Radiographic findings of CMV ventriculoencephalitis are nonspecific. MRI findings occasionally reveal diffuse cerebral atrophy, ventriculomegaly, and hyperintensities in white matter and enhancement around the lateral ventricles, septum pellucidum, corpus callosum, and fornices. Because of the nonspecificity of MRI, the diagnosis of CMV ventriculoencephalitis must be confirmed by histological identification of inclusion-bearing cells, the so-called “Owl’s eye” cells [19, 23, 24].

The prognosis for CMV ventriculoencephalitis is very poor. In published cases, 14 of 16 patients, (15/17 including ours) died despite administration of antiviral therapy. The lack of antiviral efficacy may be because of (a) the prolonged interval between initiation of treatment and onset, (b) low drug penetration into CSF (GCV and FCV penetrate, respectively, 24%–67% and 11%–47%) [25, 26], and (c) viral mutations conferring resistance to drugs. In fact, the majority of the AIDS patients and those receiving HSCT harbor viruses resistant to GCV [8, 27, 28]. Among all 15 published cases (only 2 patient did not receive GCV) including ours, reported evidence either of GCV-resistant mutants or increased levels of CMV viremia that could be considered consistent with GCV resistance.

We did not determine whether GCV-resistant strains were present in our case. Mutations in the virus-encoded UL97 kinase and UL54 DNA polymerase genes confer GCV resistance. GCV, a guanosine analog, is inactive, and requires UL97-mediated phosphorylation to get converted to its active form, which is incorporated into viral DNA by the viral DNA polymerase. FCV, a pyrophosphate analog, does not require intracellular activation, whereas CDV, a monophosphate analog, requires diphosphorylation by cellular kinases for activation, but not by viral kinases expressed by CMV early genes. The activities of both drugs are affected by DNA polymerase mutations, such as UL54 [28]. In 16 patients with such mutations, UL97, UL54, and UL97 plus UL54 mutations were detected in 6, 2, and 1 patients, respectively. Only 2 out of the 7 cases with UL97 mutations survived. One survivor was treated with a

combination of FCV and CDV after initial therapy with GCV and i.v. Ig [12]. The other survivor received leflunomide, CDV, i.v. Ig, and CMV-specific i.v. Ig, and 4 unmanipulated donor lymphocyte infusions (U-DLI). All cases with the UL54 mutation died.

Akpek et al. reported that nonspecific U-DLI might possess clinical activity against drug-resistant CMV, possibly resulting from the reactivation and expansion of CMV-specific cytotoxic memory T cells in donor lymphocytes *in vivo* [15]. CMV-specific cytotoxic T cells are known to prevent development of severe CMV disease after HSCT [29]. Indeed, 14 of 17 patients developed CMV CNS disease after receiving T cell-depleted HSCT, or ATG, or both. Moreover, a low CD4 count (≤ 70) was observed in all 13 patients (excluding the 4 patients not assessed).

The most likely causes of immunosuppression in our case were the use of ATG, CBT, a very low CD4 count, and recurrent CMV viremia. There is compelling evidence to implicate the following risk factors in the development of CMV CNS disease: severe and protracted T-cell immunodeficiency (such as T-cell depletion, ATG, and CBT), GVHD presenting concurrently with CMV CNS disease, and a history of previous recurrent CMV viremia [13]. It is very difficult to diagnose the potential of a patient for developing CMV CNS, which, of course, makes it equally difficult to design and implement an appropriate therapy. Several clinical therapies have been attempted in previous cases, however most including that attempted in our case failed. One survivor received CDV and another received U-DLI combined with CDV. In our case, U-DLI could not be administered because we used CBT to overcome donor incompatibility issues. Further, CDV is not available in Japan. Hence we could not take advantage of the therapeutic options that resulted in successful outcomes. On the basis of our case reported here and those published by others, it is clear that combination therapy with antivirals such as i.v. Ig, and U-DLI, should be considered because single anti-viral agents lack efficacy.

Conflict of interest

The authors declare no conflict of interest.

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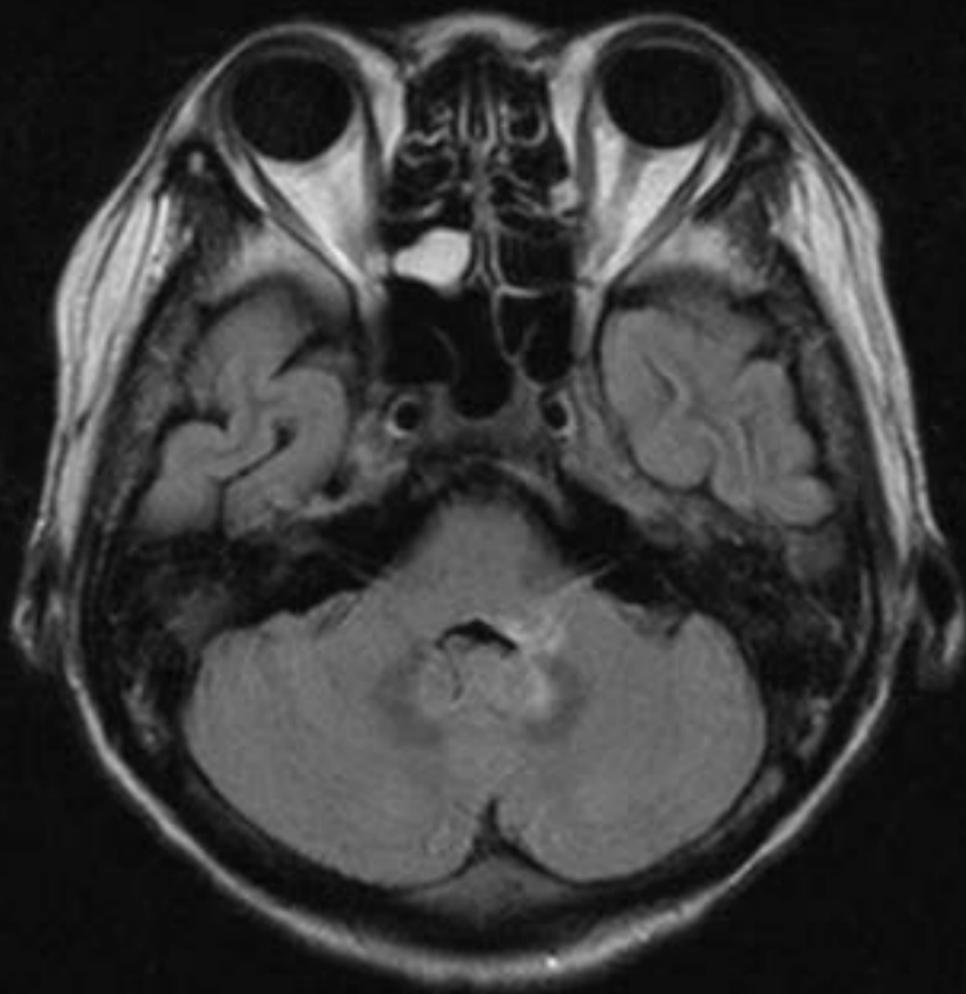
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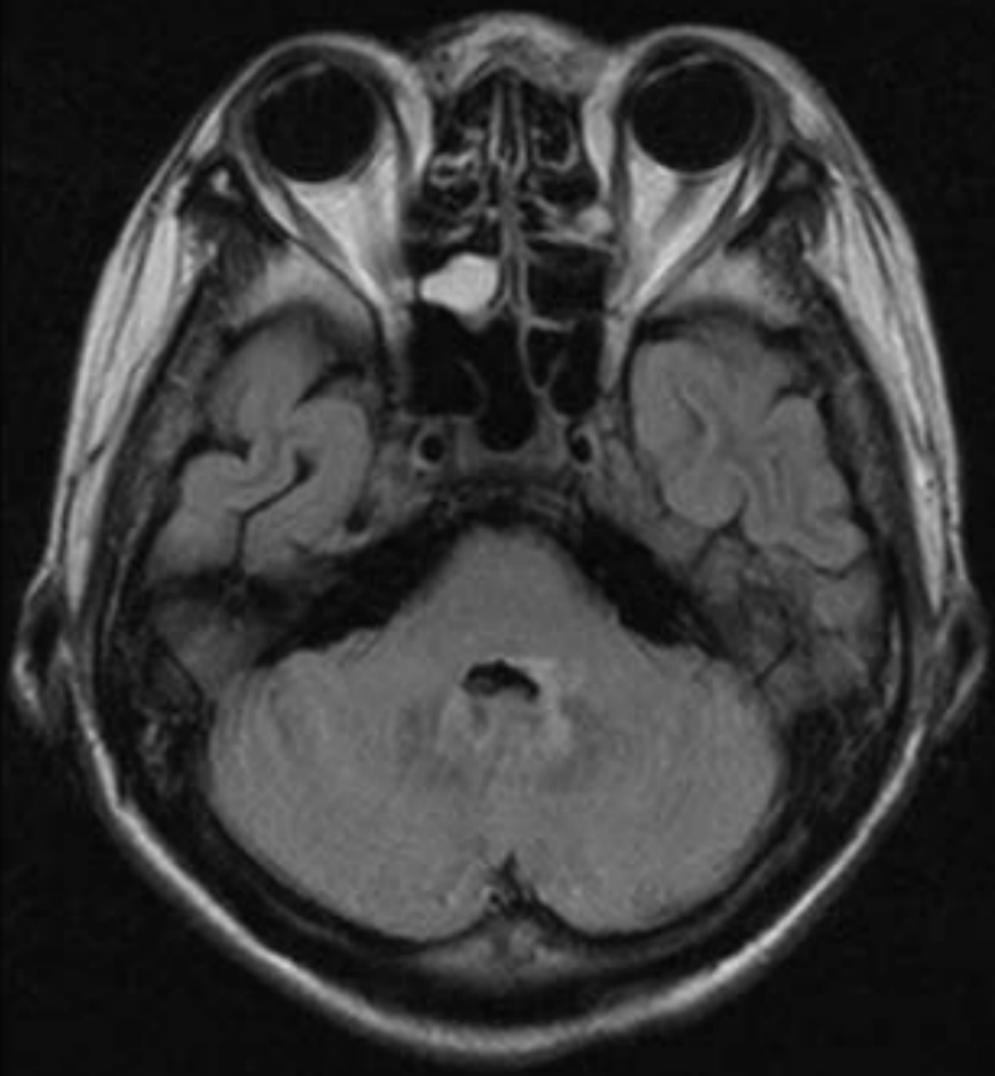
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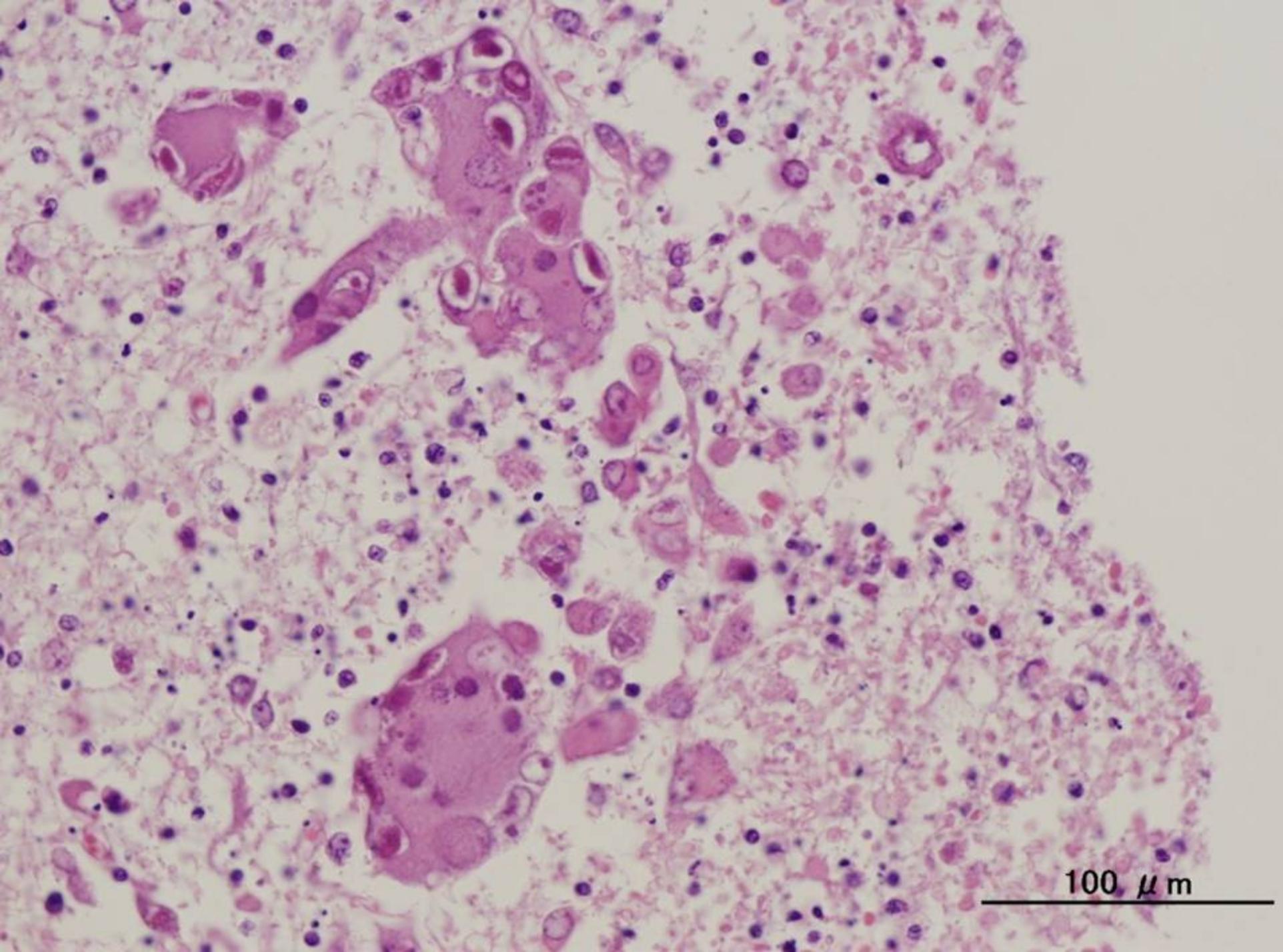
Fig. 1 CMV ventriculoencephalitis. All data shown here were acquired after the third round of CBT. (A) MRI on day 122 showed hyperintense lesions by T2-weighted image MRI. (B) On day 148, the lesions diminished as assessed by FLAIR. (C) On day 157, MRI showed hyperintense lesions around the left vestibulocochlear nerve in addition to the previous lesions detected by FLAIR.

Fig. 2 (A) Histopathological analysis demonstrated numerous inclusion-bearing cells in the anterior horn of the left lateral ventricular tissues. (B) Histopathological analysis of the central body of left lateral ventricular tissues. (C) Detection of CMV-positive cells by immunolabeling. (D) The central body of right lateral ventricular tissues was analyzed by histopathology and (E) immunolabeling with an anti-CMV antibody.



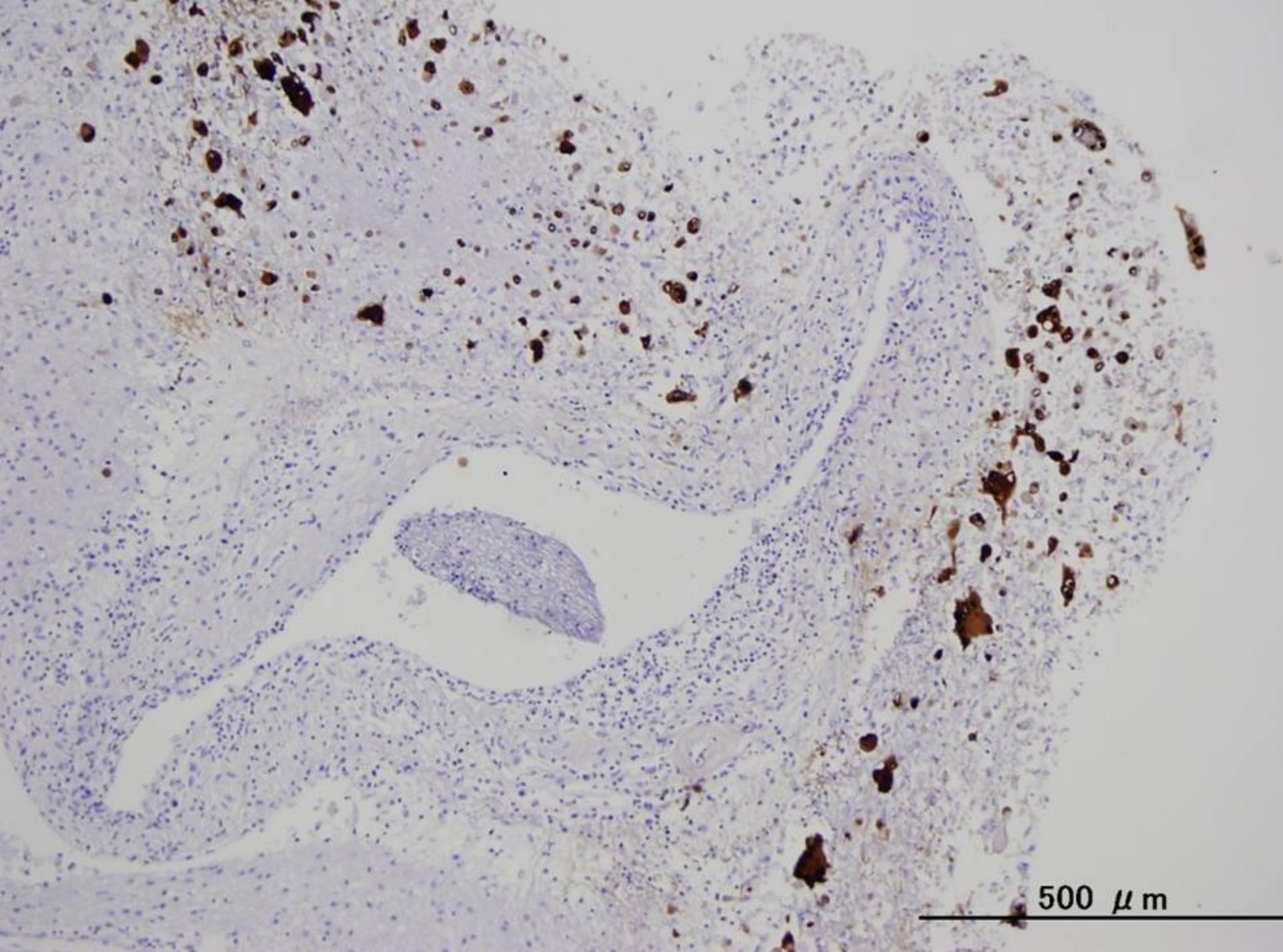




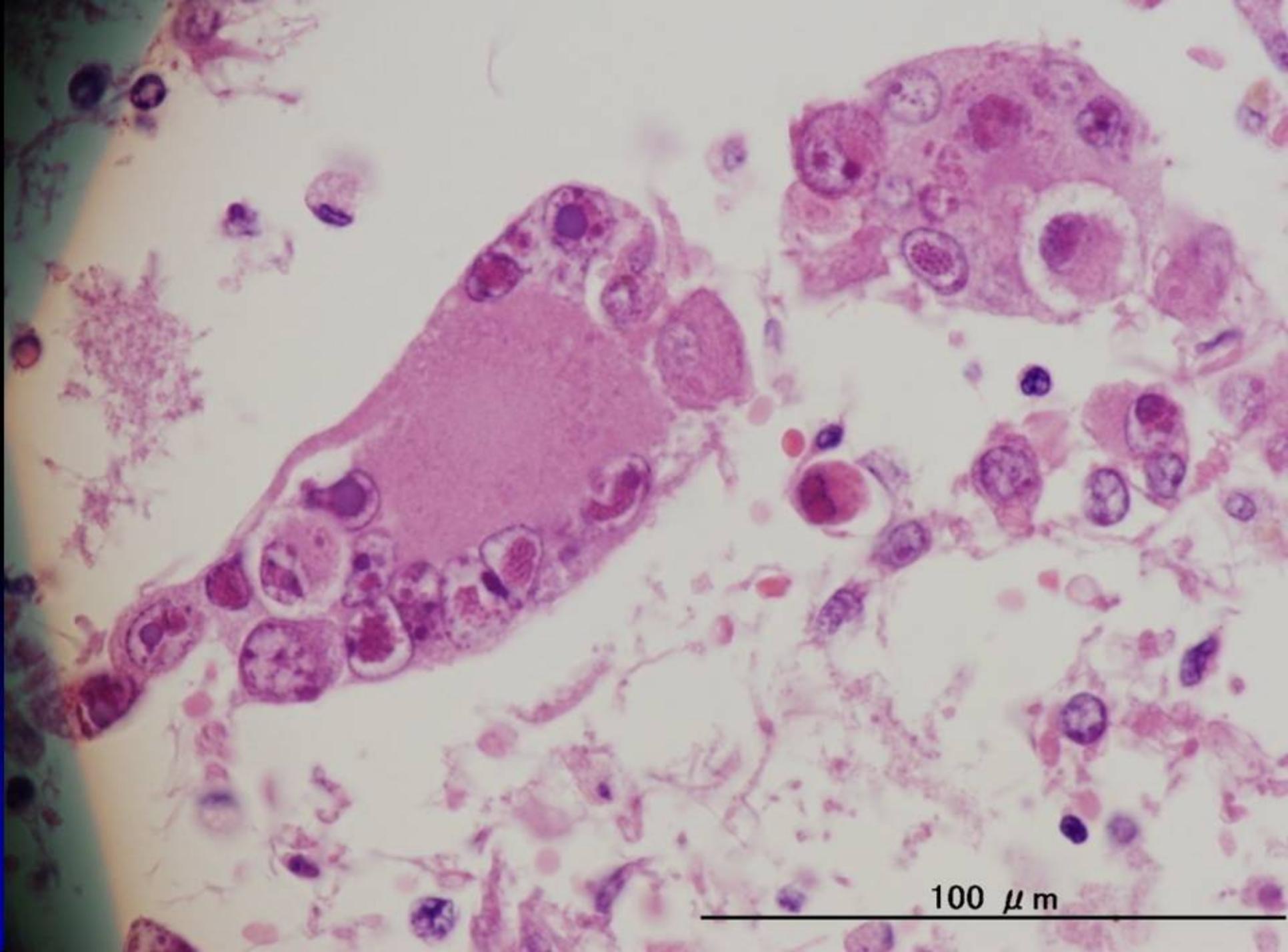




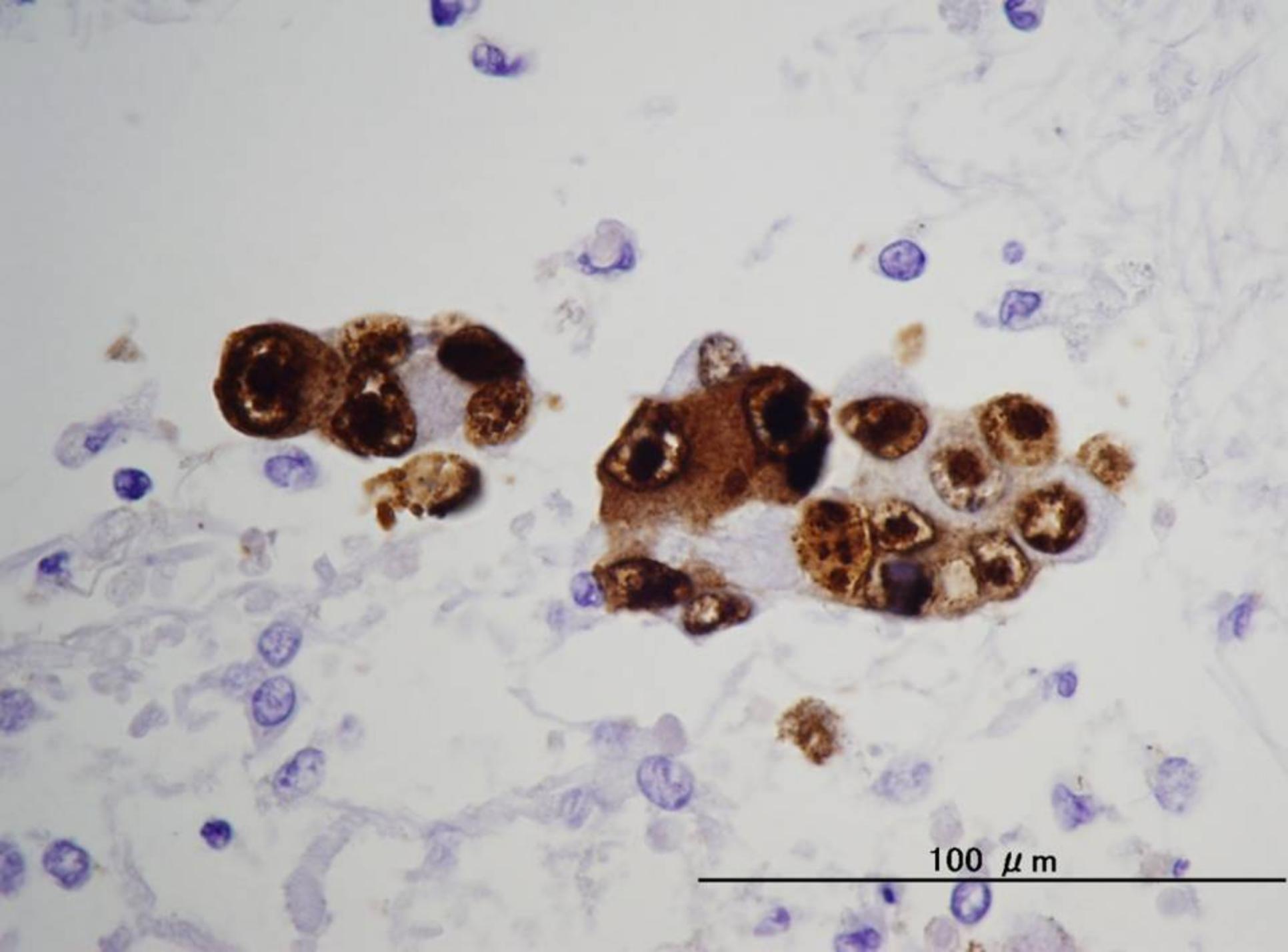
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