CASE

CNS atypical T-cell lymphoproliferative disease following treatment with alemtuzumab

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Alemtuzumab is a humanized anti-CD52 monoclonal antibody used to treat refractory relapsing-remitting MS (RRMS). Although it is a highly efficacious therapy, it has several side effects including infusion reactions, secondary autoimmune disease, infections, and malignancy.[1] Recently, there have been cases of a severe reactivation of MS disease activity due to reconstitution of CD20-positive B lymphocytes.[2] We report a case of a 41-year-old woman with worsening cognitive decline, alopecia, progressive weakness, vision loss, and seizures 16 months after initiation of alemtuzumab who succumbed to her CNS atypical T-cell monoclonal lymphoproliferative disease as a complication of therapy.

PRACTICAL IMPLICATIONS

Autoimmune disease is a well-recognized complication of alemtuzumab therapy in MS; however, the risk of subsequent malignancy is another important consideration in this highly efficacious therapy. Here, we report a fatal atypical T-cell hematologic disorder.

Case report

A 41-year-old woman with a previous diagnosis of RRMS presented with a steady decline after initiation of alemtuzumab therapy. The patient initially presented to an outside neurology provider in 2011 with optic neuritis. The diagnosis of RRMS was based on brain MRI and clinical symptoms. Because of symptom progression, disease-modifying therapy (DMT) was escalated over 5 years including the use of glatiramer acetate, dimethyl fumarate, and rituximab. The patient received her first dose of alemtuzumab in May 2016 and second dose in May 2017, shortly before moving to Colorado and establishing care.

Approximately 4 months after her second infusion of alemtuzumab, the patient experienced cognitive dysfunction, alopecia, progressive weakness, visual changes, diffuse skin rash, and seizures prompting further workup. Brain MRI was obtained, demonstrating new confluent posterior patchy T2 hyperintensities with enhancement (figure 1A). CSF revealed 71 white blood cells (70% eosinophils) with negative infectious studies including Epstein-Barr virus, polymerase chain reaction (PCR), and John Cunningham virus PCR. HIV was negative. Autoimmune evaluation included a negative CSF and serum autoimmune encephalopathy evaluation with testing for glial fibrillary acidic protein antibodies (Mayo Clinic Laboratories). Ocular examination and body positron emission topography were unremarkable. Cutaneous skin biopsy showed "spongiotic dermatitis with eosinophils," and brain biopsy of her left occipital lobe lesion showed a massive cytologically atypical but not monomorphic cytologically (as in T-cell lymphoma) $CD3^+$ T-cell positive lymphoproliferative process (figure 2). CD4 T cells predominated over CD8 T cells, and T-cell next-generation sequencing (NGS) showed a biallelic monoclonal T-cell population. She continued to worsen, and a second brain biopsy of the left occipital lobe 2.5 months later showed histologic features and T-cell gene rearrangement identical to the first biopsy. Cytogenetic assessment and fluorescence in situ hybridization were negative for 5′PDFGB (5q33.1)/3′PDGFRB (5q33.1) 3′; 5′TCRG (7q34)/3′TCRB (7q34), 5′FGFR1 (8p11)/3′FGFR1/8, 5′TCRAD (14q11)/3′TCRAD (14q11), or 5′TCL1 (14q32)/3′TCL1 (14q32) rearrangements.

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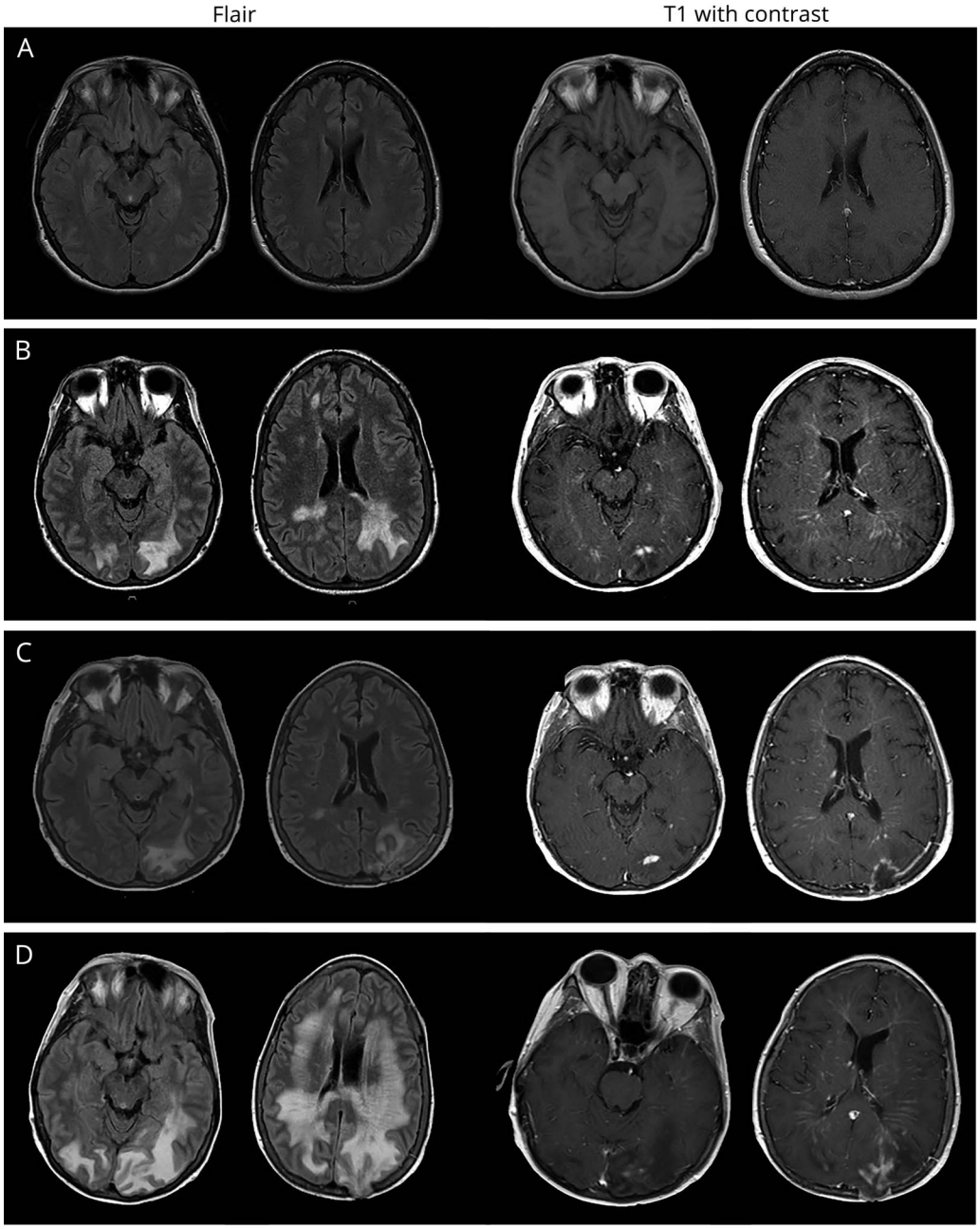
Figure 1 MRI before and after treatment with alemtuzumab therapy

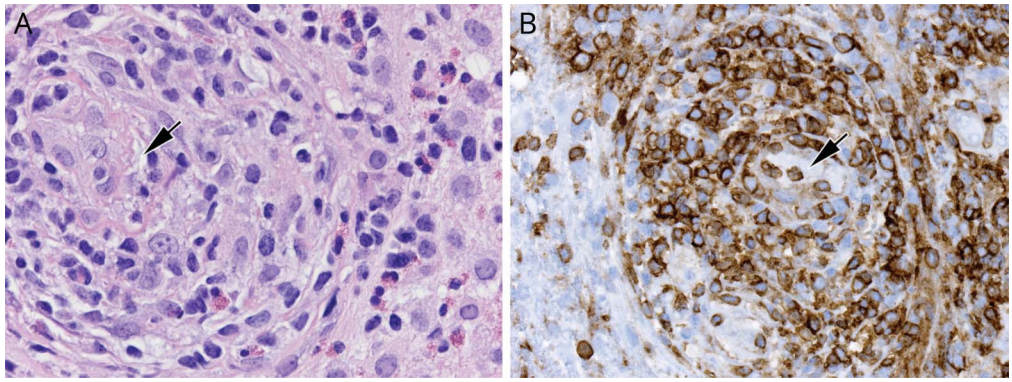


(A) MRI 8 months before treatment with alemtuzumab therapy. There was no evidence of previous T2 lesions or enhancing lesions in similar locations before initiation of alemtuzumab. (B) MRI 18 months after alemtuzumab therapy. Fluid-attenuated inversion recovery (FLAIR) images demonstrate progressive confluent, asymmetric white matter hyperintensities with patchy enhancement most severe in the left parietal lobe. Shortly after, started on rituximab infusions at 500 mg/m^2 weekly infusions and high-dose steroids. (C) MRI 22 months after alemtuzumab and after parietal lobe biopsy (see Figure 2 for pathology demonstrating a T-cell lymphoproliferative disease) (D) MRI 24 months after alemtuzumab therapy. Imaging after treatment with rituximab, high-dose methotrexate, procarbazine, vincristine, methylprednisolone, and cytosine arabinoside with diffuse worsening of FLAIR hyperintensities.

Bone marrow sampling demonstrated the T-cell receptor gene clone previously identified by NGS by aspirate, but the atypical T-cell lymphoproliferative was not well captured on the core. Nevertheless, this indicated a systemic effect of the drug.

The biopsy was most consistent with lymphoproliferative disease (not a T-cell lymphoma) from a pathological standpoint; however, given the atypical features, monoclonal T-cell population, and malignant clinical course, the patient was treated aggressively for a T-cell lymphoma or pre-T-cell lymphoma. The patient was treated with rituximab, high-dose methotrexate, procarbazine, vincristine, methylprednisolone, and cytosine arabinoside with little improvement. Brain MRI 24 months after initial alemtuzumab induction demonstrated worsening perivascular enhancement and new diffusion

Figure 2 Brain biopsy pathology



(A) The first biopsy demonstrated perivascular and parenchymal infiltration by cytologically atypical, but not monomorphic, enlarged lymphocytes; note the accompanying eosinophils at right in A, as are often found in T-cell processes. Hematoxylin and eosin, 600×. (B) The atypical lymphoproliferative disorder showed a predominance of CD4-positive T cells; only rare B cells were found. Immunostaining for CD4 with light hematoxylin counterstain, 400× (arrows indicate the vessel lumen).

abnormalities (figure 1C). Despite therapy, the patient worsened clinically. Because of disease progression, she transitioned to supportive care with palliative whole-brain radiation. She succumbed to her disease 10 months after initial presentation.

Discussion

To our knowledge, this is the first report of CNS atypical T-cell lymphoproliferative disease in the setting of alemtuzumab therapy. Alemtuzumab is a monoclonal IgG1 antibody that targets the human CD52 protein expressed on T and B lymphocytes, resulting in their depletion. After administration, a reconstitution process occurs with B lymphocytes returning within 3 months. The repopulation of the $CD8^+$ and $CD4^+$ T cells takes considerably longer, with a timeline of 31 and 60 months, respectively.[3] There are several documented cases of autoimmune disorders (e.g., thyroid disease, immune thrombocytopenic purpura, and glomerulonephritis) thought to be due to the rapid reconstitution of B-cell population. The prolonged $CD4^+$ T-cell lymphopenia, however, much like in cases of primary CNS lymphoma arising in those with HIV, may be a proposed mechanism for the unchecked proliferation of malignant cells.

Other malignancies observed with alemtuzumab therapy include breast cancer, non–EBV-associated Burkitt lymphoma, and cervical cancer in CAMMS223.[4] Between CARE-MSI and CARE-MSII, 17 alemtuzumab-treated patients developed malignancies.[5,6] In the extension study of CAMMS223, 1 patient developed systemic Castleman disease, a prelymphomatous state resulting in the activation of plasma cells.[7] There have been no previously reported cases of primary CNS lymphoma within alemtuzumab treatment populations. Notably, this patient was previously on other DMTs before alemtuzumab including glatiramer acetate, dimethyl fumarate, and rituximab, and to our knowledge, there have been no previous reports of primary CNS lymphoma with these agents; it had been at least 2 years since the patient received rituximab. Although we cannot rule the effects of these DMTs or an additive effect of these DMTs, given the mechanism of action of alemtuzumab, previous malignancies reported with alemtuzumab including systemic lymphoma, and the time course of presentation, our suspicion is that alemtuzumab was a large contributor to this patient's presentation.

Alemtuzumab can be an effective DMT in the treatment of RRMS; however, strict and rigorous monitoring is critical. CNS atypical T-cell lymphoma can be a serious adverse event after alemtuzumab therapy and should be considered as a potential fatal outcome in treated patients.

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Appendix Authors

Name	Location	Role	Contribution
Murtaza Khan, MD	University of Colorado School of Medicine, Aurora, CO	Author	Drafted the manuscript for intellectual content and direct patient care
Douglas E. Ney, MD	University of Colorado School of Medicine, Aurora, CO	Author	Revised the manuscript for intellectual content and direct patient care
Bette K. Kleinschmidt-DeMasters, MD	University of Colorado School of Medicine, Aurora, CO	Author	Revised the manuscript for intellectual content and pathology images
Lindsay Horton, MD	University of Colorado School of Medicine, Aurora, CO	Author	Revised the manuscript for intellectual content
Enrique Alvarez, MD, PhD	University of Colorado School of Medicine, Aurora, CO	Author	Revised the manuscript for intellectual content
Amanda L. Piquet, MD	University of Colorado School of Medicine, Aurora, CO	Author	Drafted and revised the manuscript for intellectual content and direct patient care

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