

JAMA Clinical Challenge

Multiple Cerebral Infarctions and Intracranial Vessel Abnormalities

Eline A. Oudeman, MD; Catharina J. M. Frijns, MD, PhD; Catharina J. M. Klijn, MD, PhD

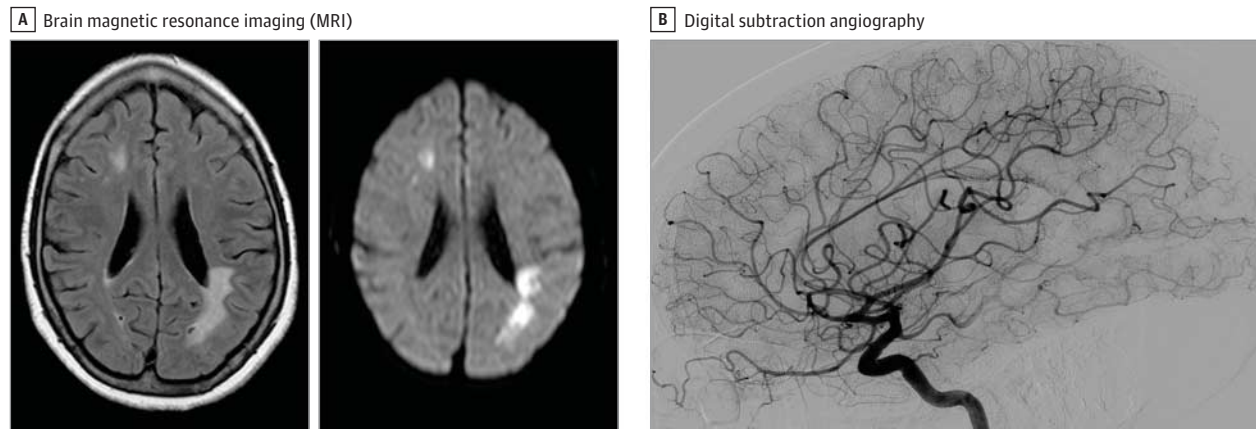


Figure 1. A, Axial MRI using fluid-attenuated inversion recovery (left) demonstrating hyperintense multifocal lesions involving mainly the subcortical white matter; axial diffusion-weighted MRI (right) showing hyperintense lesions consistent with recent infarctions. B, Digital subtraction angiography of the

intracranial vessels showing widespread areas of vessel wall irregularity, which consist of zones of focal stenosis and luminal tapering in many third-order and fourth-order branches.

Several months before being admitted to the hospital, a 65-year-old woman noted relapsing fevers, night sweats, fatigue, and a 16-kg weight loss. In the weeks before her hospital admission, she developed



Quiz at jama.com

subacute cognitive deterioration and progressive headaches. On presentation she has difficulties initiating speech (non-fluent aphasia) and responds slowly and inconsistently to questions. Otherwise, her physical examination is unremarkable. Laboratory studies reveal an elevated erythrocyte sedimentation rate (ESR) (135 mm/h), anemia (hemoglobin level, 9.5 g/dL), and high serum levels of soluble interleukin 2 receptor (sIL2R) (36 551 pg/mL), lactate dehydrogenase (LDH) (448 U/L), and β_2 -microglobulin (3.1 mg/L), with normal renal function, liver enzyme levels, and serum immunological and microbiological findings. Analysis of the cerebrospinal fluid (CSF) demonstrates a mildly increased leukocyte count ($11 \times 10^6/L$) and total protein concentration (0.10 g/dL). Magnetic resonance imaging of the brain shows multiple infarctions, and digital subtraction angiography of the intracranial vessels demonstrates abnormalities suggestive of vasculitis (**Figure 1**). An electrocardiogram, computed tomography scans of the chest and abdomen, 18-fluorodeoxyglucose positron emission tomography, transesophageal echocardiography, inspection of the skin, and ophthalmologic evaluation are unremarkable.

WHAT WOULD YOU DO NEXT?

- A. Initiate secondary preventive treatment for multiple infarctions with antiplatelet agents.
- B. Initiate treatment for cerebral vasculitis with corticosteroids.
- C. Postpone treatment; obtain a brain biopsy including the leptomeninges.
- D. Postpone treatment; obtain random skin biopsies and a bone marrow biopsy.

Diagnosis

Intravascular large B-cell lymphoma of the central nervous system (CNS).

What to Do Next

D. Postpone treatment; obtain random skin biopsies and a bone marrow biopsy.

The key clinical features in this case are the need for pathological confirmation of the diagnosis and the low positive predictive value of digital subtraction angiography for cerebral vasculitis. In addition to the neurologic findings, the presence of systemic illness and laboratory findings suggest a diagnosis of intravascular CNS lymphoma. This diagnosis can be confirmed with skin or bone marrow biopsy.^{1,2}

Discussion

Intravascular large B-cell lymphoma is a systemic disease typically occurring in elderly patients (median age, 67 years).² Previously known as "neoplastic angioendotheliomatosis," the disease is characterized by multifocal proliferation of pleomorphic large lymphoid cells within medium to small vessels.³ Vessel walls and tissues surrounding the involved vessels are spared, and lymphadenopathy is usually absent.³ The tumor may possibly originate from post-germinal center cells.² Immunophenotyping usually identifies the tumor cells as mature B cells, although there are reports of T-cell or natural killer-cell tumor types.²

In Western countries, the CNS and skin are most frequently involved, although almost every other organ can be affected.^{2,4} Fifty-five percent to 85% of patients present with constitutional B-cell symptoms (fevers, night sweats, and weight loss) together with symptoms attributable to occlusion of small vessels of affected organs.⁵ CNS involvement can present as focal neurologic deficits, alteration of consciousness, seizures, or rapidly progressive dementia. The most common laboratory abnormalities are anemia, elevated ESR, and elevated serum levels of sIL2R, LDH, and β_2 -microglobulin.² With intravascular CNS lymphoma, analysis of CSF usually shows a mildly increased leukocyte count and protein concentration. Flow cytometric immunophenotyping and conventional cytologic examination of the CSF are typically unrevealing.

The diagnosis of intravascular large B-cell lymphoma is confirmed by cutaneous lesion or random biopsy of normal skin, bone marrow biopsy, or biopsy of other sites of suspected involvement such as the brain.^{2,6} Because vessels containing intravascular lymphoma are mainly located in the subcutaneous fat, subcuticular tissues should be included in skin biopsies.⁶ Patients with vascular disease are frequently treated with antiplatelet agents, but these should be avoided if brain biopsy is being considered. Corticosteroids may mask clinical

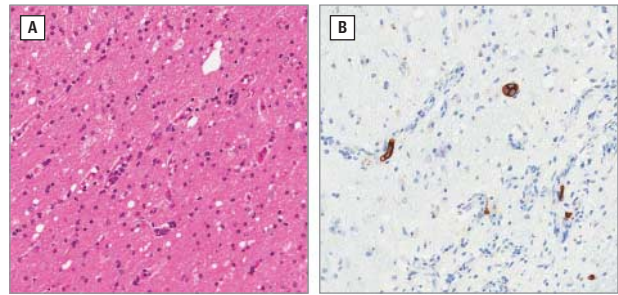


Figure 2. Left occipital brain biopsy specimen (original magnification $\times 200$). A, Hematoxylin-eosin stain showing large, atypical, pleomorphic cells with large nuclei within the capillaries. B, Tumor cells in the vessel are highlighted (brown) by immunohistochemical staining for CD20 capillaries.

cal symptoms and may reduce the chances of identifying the pathology in biopsy specimens. Awaiting the effect from these treatments will also lead to a delay in diagnosis.

Because intravascular lymphoma is not common and has inconsistent clinical presentations, it is often difficult to establish the diagnosis antemortem.⁵ Because clinical trials for intravascular large B-cell lymphoma are lacking, treatment recommendations are based on results from studies of other, more common lymphomas. Treatment for intravascular lymphoma usually consists of cyclophosphamide, doxorubicin, vincristine, prednisone, and the recombinant anti-CD20 antibody rituximab (R-CHOP). Intrathecal chemotherapy (prophylactic or therapeutic) directed toward the CNS is also appropriate.^{2,3} The prognosis of intravascular lymphoma has improved since the addition of rituximab to chemotherapy. Three-year survival rates now range from 53% to 81%.² Long-term survival is possible and is more likely when the diagnosis is made early and treatment is initiated early.²

Patient Outcome

Deep skin biopsies at 2 different locations of clinically unaffected skin and bone marrow biopsy showed no abnormalities. A biopsy of the left occipital lesion demonstrated proliferation of large atypical lymphoid cells in the vessels, producing luminal obstruction surrounded by necrotic lesions consistent with cerebral infarctions (Figure 2A). The neoplastic cells were positive for CD20 and CD79a and negative for CD5 (Figure 2B), which confirmed the diagnosis of intravascular large B-cell central nervous system lymphoma. The patient was treated with R-CHOP chemotherapy and intrathecal methotrexate. Her aphasia and cognitive functioning improved within several days after treatment initiation. After 6 months, her aphasia had recovered almost completely, but some residual cognitive impairment persisted.

ARTICLE INFORMATION

Author Affiliations: Department of Neurology and Neurosurgery, Brain Center Rudolf Magnus, University Medical Center Utrecht, the Netherlands.

Section Editor: Huan J. Chang, MD, Associate Editor.

Corresponding Author: Eline A. Oudeman, MD, Department of Neurology and Neurosurgery, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, the Netherlands (e.a.oudeman@gmail.com).

Conflict of Interest Disclosures: The authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Klijn reported receiving grants from the Netherlands Heart Foundation and the Brain Foundation. No other disclosures were reported.

Additional Contributions: We thank L. J. Kappelle (Brain Center Rudolf Magnus) for his thoughtful reviews of the manuscript and W. G. M. Spliet (Department of Pathology, University Medical Center Utrecht) for his help in analyzing the specimens. We thank the patient and her guardian for providing permission to share her information.

REFERENCES

1. Kadkhodayan Y, Alreshaid A, Moran CJ, et al. Primary angitis of the central nervous system at conventional angiography. *Radiology*. 2004;233(3):878-882.
2. Shimada K, Kinoshita T, Naoe T, Nakamura S. Presentation and management of intravascular large B-cell lymphoma. *Lancet Oncol*. 2009;10(9):895-902.

3. Zuckerman D, Seliem R, Hochberg E. Intravascular lymphoma: the oncologist's "great imitator." *Oncologist*. 2006;11(5):496-502.

4. Ponzoni M, Ferreri AJ, Campo E, et al. Definition, diagnosis, and management of intravascular large B-cell lymphoma. *J Clin Oncol*. 2007;25(21):3168-3173.

5. Ferreri AJ, Campo E, Seymour JF, et al. Intravascular lymphoma. *Br J Haematol*. 2004;127(2):173-183.

6. Matsue K, Asada N, Odawara J, et al. Random skin biopsy and bone marrow biopsy for diagnosis of intravascular large B cell lymphoma. *Ann Hematol*. 2011;90(4):417-421.