

Progressive multifocal leuko-encefalopathy after treatment with rituximab and fludarabine

M.L Erkamp; S.A. Luykx - de Bakker

tergooiziekenhuizen

Past medical history

2006: Low grade follicular B cel NHL stage IIIA

2007: Progressive disease; 8x R-CVP: remission, rituximab maintenance treatment

2008: Relapse; 6x FCR: complete remission

2009: Gegeneralised Herpes zoster, CMV colitis

Out patient clinic april 2009

Presenting complaint: word finding difficulties and decreased acuity in the left eye

Neurological examination: Broca's aphasia, visual acuity of the left eye 0.05, slowed pupillary reaction to light with loss of conjugate movement in the left lateral gaze

Differential diagnosis: ischemic CVA, spread of NHL to the central nervous system

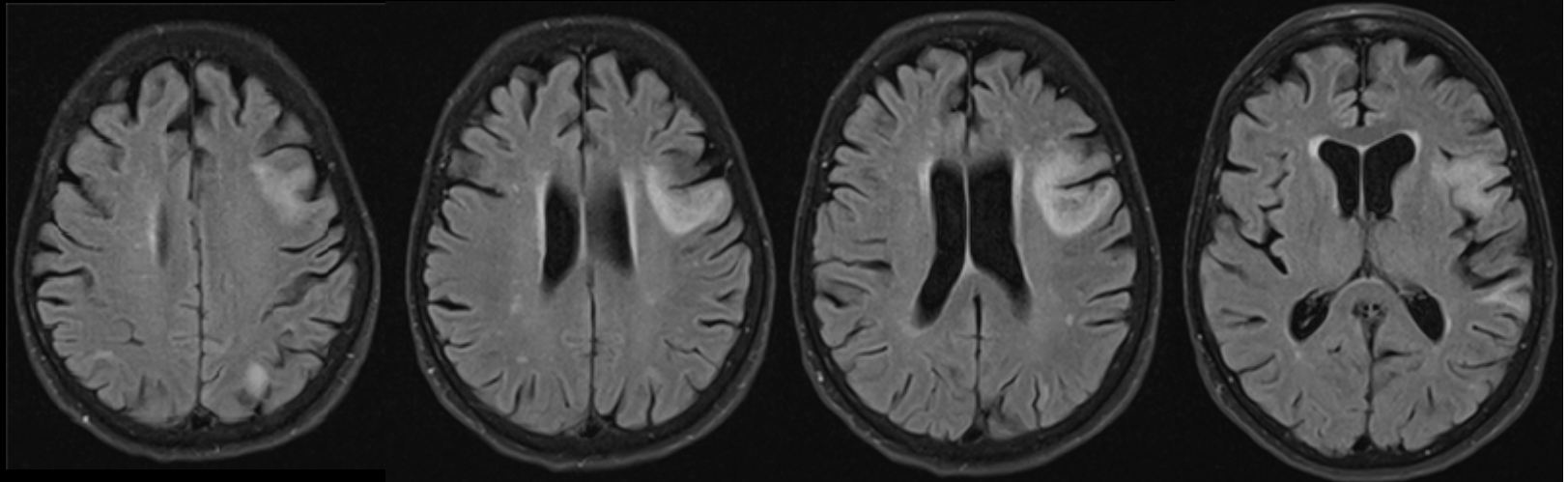


CT brain: left parietal subcortical hypodense lesion

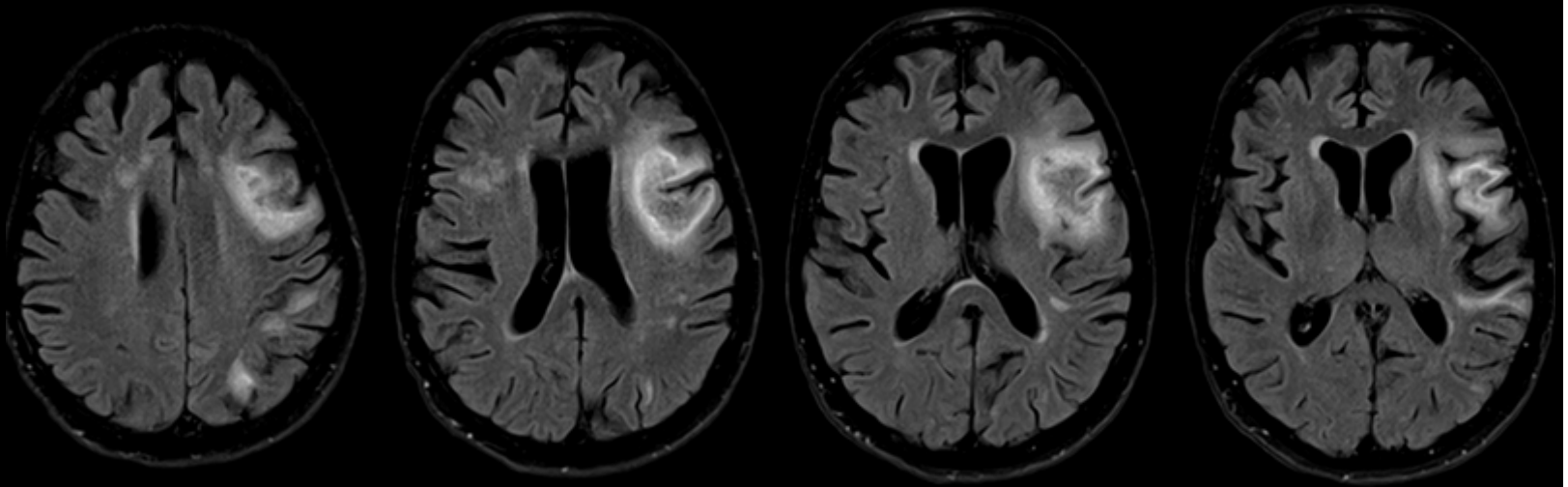
Spinal tap: protein 0.25 g/L, 3×10^6 /L leukocytes, T lymphocytes, no B lymphocytes

MRI brain

April 2009



May 2009





MRI brain: multifocal white matter lesions

Spinal tap: PCR detected JC virus

Diagnosis: PML

Rapidly progressive demyelinating leukoencephalopathy

Varying clinical presentation depending on disease localization

Destruction of oligodendrocytes with loss of myelin through primary infection or reactivation of JC virus

Median survival months

Diagnosis: clinical course, MRI and PCR spinal fluid

JC virus

1958 PML first described by Astrom in patients with CLL and Hodgkin lymphoma

1967 discovery of JC polyoma virus by Zu Rhein

Mainly CD4 en CD8 lymphocytopenia caused by:

HIV

Immunosuppressive and immunomodulating drugs

fludarabine, cyclofosfamide, methotrexate,

MMF, corticosteroids

alemtuzumab, natalizumab, rituximab

Hematological malignancies and after SCT

SLE

PML and rituximab

Over 76 cases have been reported in the literature

Case serie 57 patients with PML (Carson et al., 2009)

- 52 lymphoproliferative diseases

- 45.6% treated with a purine antagonist

- 90% mortality, better prognosis after SCT

- Median onset after last treatment 5.5 months

- Median survival after diagnosis 2 months

Incidence of PML after rituximab unknown

Treatment

Clinical recovery in HIV positive patients with HAART

Withholding immunosuppression
(plasmapheresis?, immunoadsorption?)

Cidofovir not effective

Cytarabine moderately effective, 36% stable disease (7/19)

Mirtazapine effective in in vitro studies; case reports

Mefloquine effective in in vitro studies; under investigation

Course

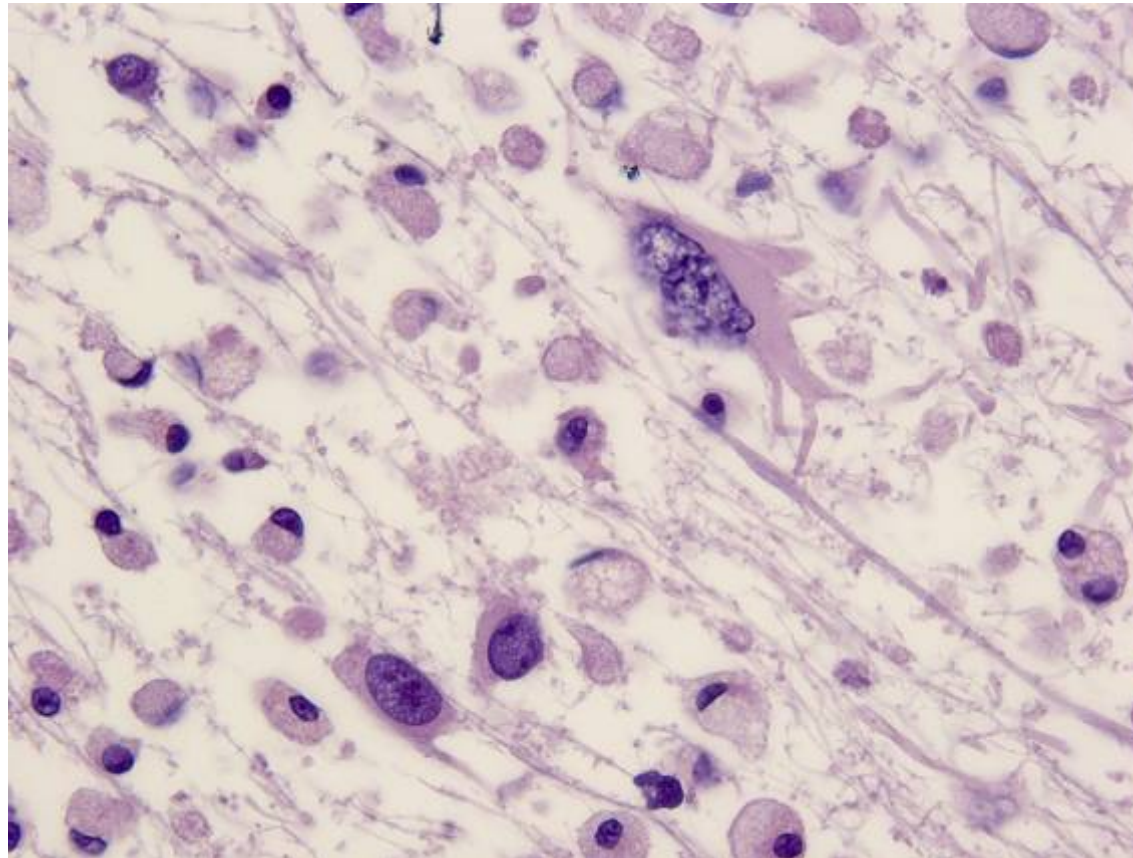
Rapidly progressive deterioration with
loss of initiative, weight loss, somnolence

Two months after presentation, the patient died

Autopsy



Autopsy



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Take home message

PML is a serious long-term complication of treatment with rituximab as well as fludarabine

New neurologic symptoms during or after treatment with rituximab should prompt consideration of PML in the differential diagnosis

Early recognition is important in order to immediately withhold immune suppression and prevent further harm

Literature

Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports projects, Carson et al., Blood; 2009; 113: 4834-40

Monoclonal antibody-associated progressive multifocal leukoencephalopathy in patients treated with rituximab, natalizumab, and efalizumab: a Review from the Research on Adverse Drug Events and Reports (RADAR) Project, Carson et al., Lancet Oncol 2009; 10: 816-24

Progressive Multifocal Leukoencephalopathy in Chronic Lymphocytic Leukemia: A report of three cases and review of the literature, D'Souza et al., 2010, Clinical Lymphoma, Myeloma and Leukemia, 10: E1-E9

Treatment of Progressive Multifocal Leukoencephalopathy Associated with Natalizumab, Wenning et al., NEJM, 2009; 361: 1075-80

Acknowledgements: professor D. Troost, neuro-pathologist, AMC, Amsterdam

