Outcome of Drug-Induced PML

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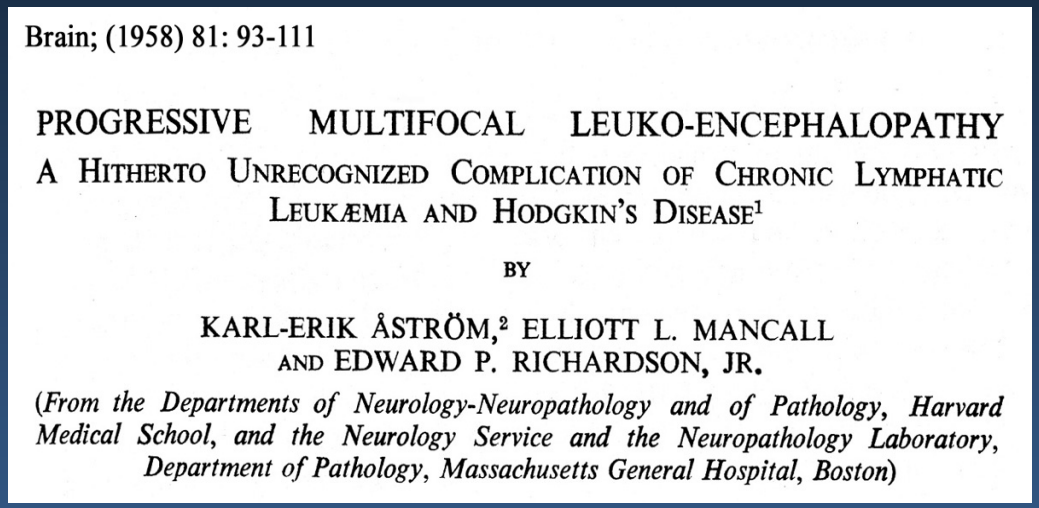
For Session 1: Overview of PML as an adverse event of immunobiologicals (MABs)
Transatlantic Workshop: Drug-related PML
London, England July 25-26, 2011

Important Considerations

- PML Epochs
  - Pre-AIDS
  - AIDS Pandemic
  - Monoclonal antibody era
- Defining Outcomes
  - Mortality
  - Morbidity

PML – The Early Years



Brain; (1958) 81: 93-111

PROGRESSIVE MULTIFOCAL LEUKO-ENCEPHALOPATHY

A HITHERTO UNRECOGNIZED COMPLICATION OF CHRONIC LYMPHATIC LEUKÆMIA AND HODGKIN'S DISEASE[1]

BY

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71 year old woman

- CLL 52 years
- L hemiparesis
- Death in 4 months

73 year old woman

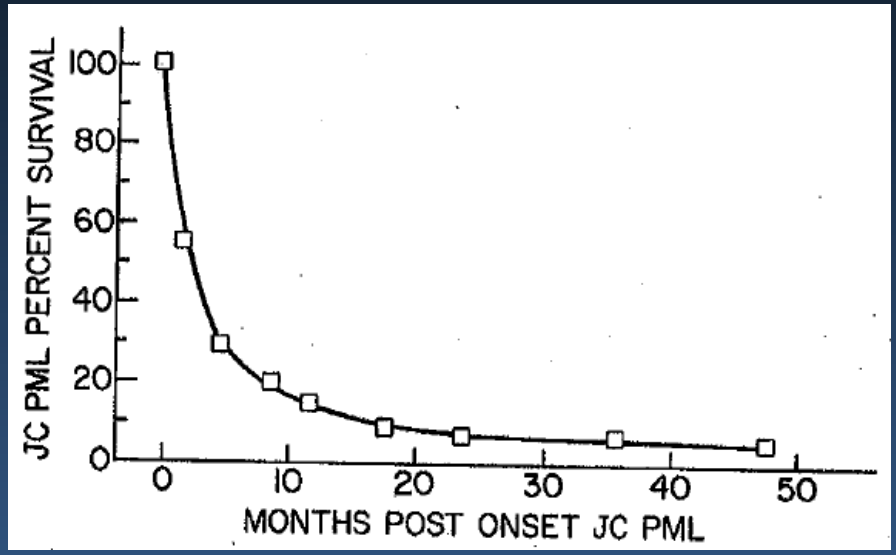
- CLL 68 years
- Unable to concentrate
- Clumsy, stupor
- Death 4 months

42 year old man

- Hodgkins disease 42
- Aphasia, hemiparesis, stupor
- Death in 10 weeks

PML Survival in the Pre-AIDS Era

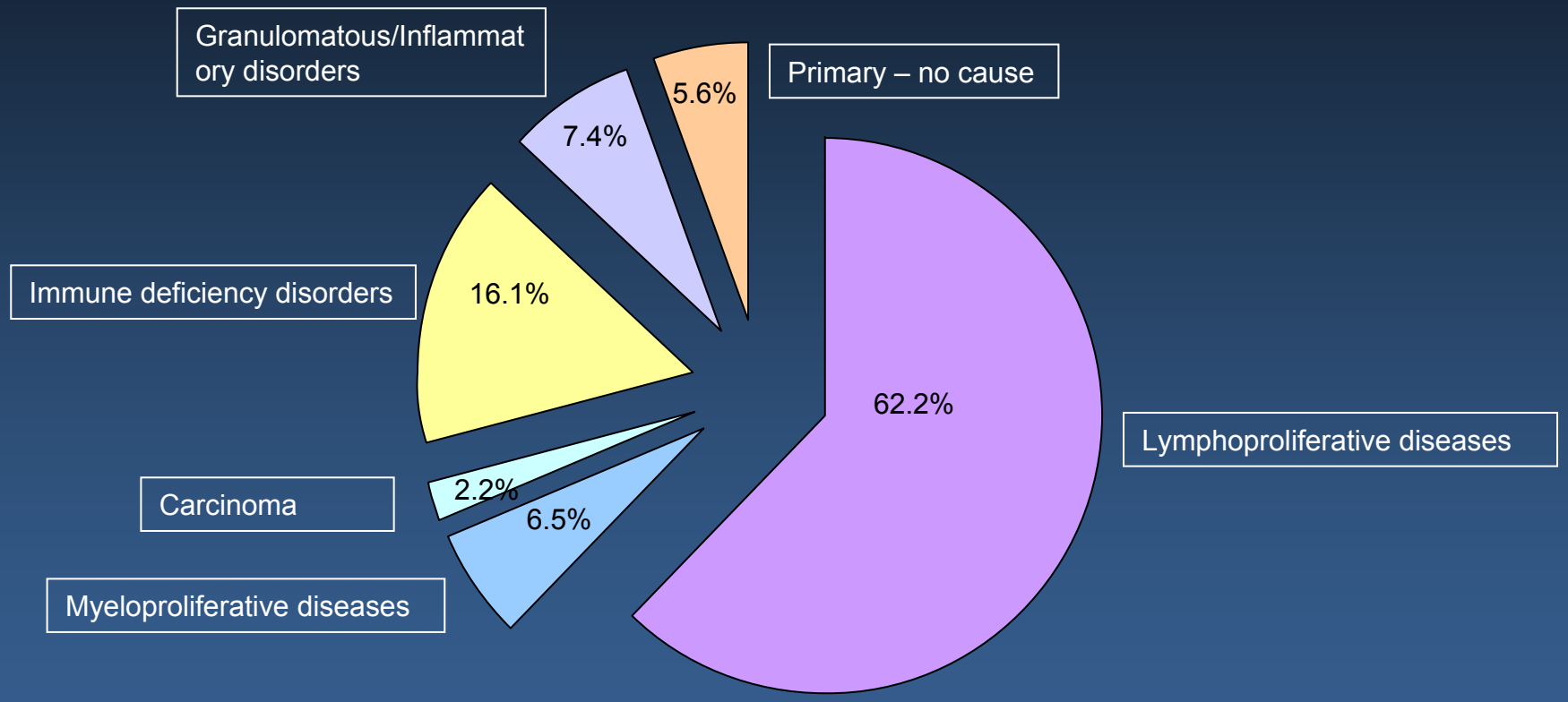
- 230 cases published and unpublished cases (1958-1984)[1]
  - 69 path confirm
  - 40 virol and path confirm
- 80% dead by 9 months of disease onset
- Longest reported survivals 5, 10, 19 years
  - Longest in virologically proven case >6 years



Survival in 54 virologically and pathologically proven cases of PML[2]

1. Brooks BR and Walker DL: Neurol Clin 1984;2:299-313. 2. Walker DL and Padgett BL in Sever JL and Madden DL: Polyomaviruses and Human Neurological Disease NY 1983

PML Survival in the Pre-AIDS Era



Brooks BR and Walker DL: Neurol Clin 1984;2:299-313

Prolonged Survival in the Pre-AIDS Era

Representative Examples

- Hedley-Whyte E.T, et al: *J Neuropath Exp Neurol* 1966;25;107-16
  - 57 year old man with lymphosarcoma
  - Transient remission and 5 year survival
  - Focal perivascular cuffing
- Stam F.C. *Psychiat Neurol Neurochir* 1966;69:453-9
  - Man with no identified underlying risk
  - 19 year survival
  - Kepes JJ, et al: *Neurology* 1975;25:1008-12
  - 46 year old man with non-tropical sprue
  - 10 year survival
  - Active perivascular inflammation

Survival of HIV-related PML Pre- and Post-HAART Eras

- Pre-HAART survival
  - Mean: 6.4 months
  - Median: 2- 6 months
  - Mode: 1-2 months
  - Survival
    - >12 months: <10%
- Post-HAART survival
  - Mean: 8.1-15 months
  - Survival
    - >12 months: 38 - 50%

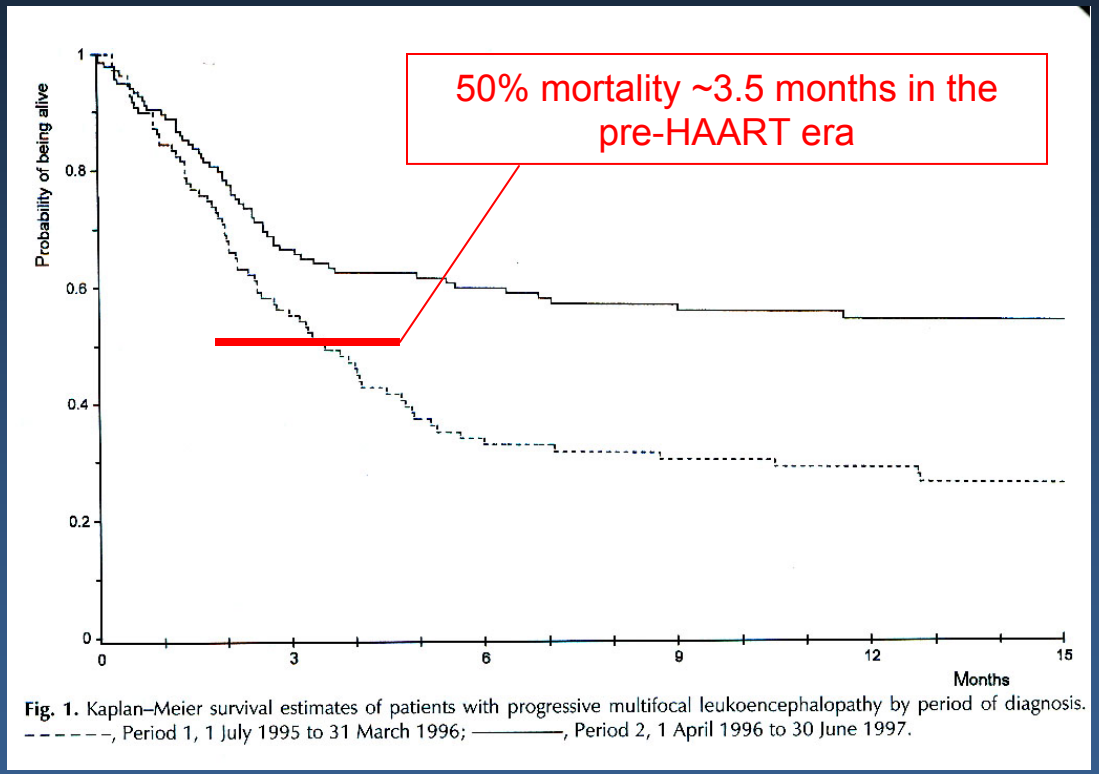
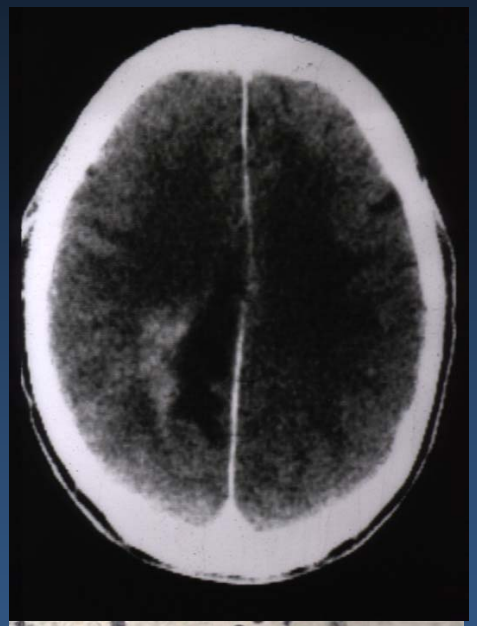


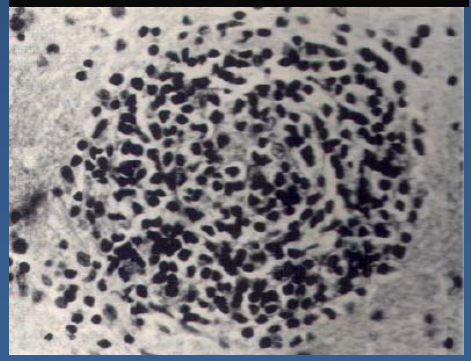
Fig. 1. Kaplan–Meier survival estimates of patients with progressive multifocal leukoencephalopathy by period of diagnosis. – – – – –, Period 1, 1 July 1995 to 31 March 1996; ————, Period 2, 1 April 1996 to 30 June 1997.

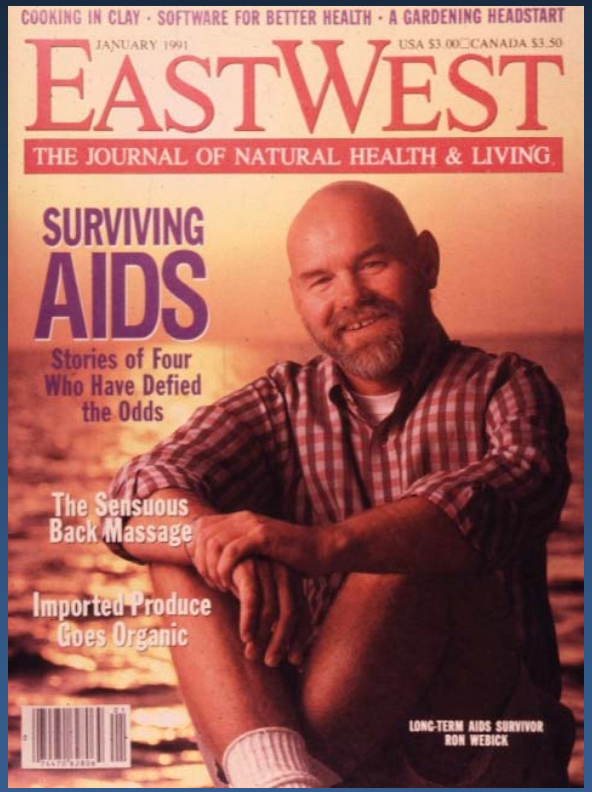
Antinori A, et al J Neurovirol 2001;7:232-8. Berger JR et al: J Neurovirol 1998;4:58-68. Falco V et al: J AIDS;49:26-31. Tassie JM, et al: AIDS 1999;13:1881-7.

PML with Long Term Survival in a HIV+ Patient

- 39 year old man
- Apr 1985 – fatigue and depression
- Jun 1985 - alien hand syndrome; clumsiness of left leg
- Jul 1985 – left hemiparesis, pseudoathetosis of LUE, severe loss of proprioception
- HIV+ ; T4/8 0.8
- Rx'd for toxo
- Bx proven PML with perivascular inflammation
- Gradual increase in CD4 from 43 (8/20/86) to 800 (5/21/97)
- Gradual neurological recovery
- Return to work
- Death at 96 months due to lymphoma after TB pericarditis
- No recurrence of PML







Berger JR and Mucke L: Neurology

PML in the Monoclonal Era

- Drugs with a unique predisposition to cause PML
  - Natalizumab
  - Efalizumab
- Drugs that increase the risk of PML in individuals with an underlying disorder predisposing to PML
  - Rituximab
  - Mycophenolate mofetil
  - Others (?)

PML in the Monoclonal Era Natalizumab

- As of July 5th, 2011[1]
  - 145 post-marketing cases of natalizumab-associated PML among 83,300 exposed patients
  - Overall risk of PML estimated to be 1.62/1000 patients (95% C.I. 1.37-1.91/1000 patients)
  - 29 of 145 (20%) have died
- Preliminary data from 79 cases collected as of December 2, 2009[2]
  - 63/79 alive
  - 38/63 with ≥ 6 month follow-up
    - ~13% with mild disability (Karnofsky 80-100)
    - ~50% with moderate disability (Karnofsky 50-70)
    - ~37% with severe disability (Karnofsky 10-40)

1. https://medinfo.biogenidec.com; 2. Gold R, et al: Neurology 2011;76 (9;Suppl 4):

Karnofsky Performance Status Scale

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

PML in the Monoclonal Era Natalizumab

- Based on first 79 postmarking PML cases
- Predictors of favorable outcome
  - Shorter time from symptom onset to diagnosis (27 v. 41 days, median)
  - Younger age (40 v. 54 years old)
  - Lower EDSS (median 3.5 v. 5.5)
  - Unilobar or multilobar (86% v. 30%)
- Not predictive
  - Gender
  - MS duration
  - Natalizumab exposure
  - Prior immunosuppressant use
  - CSF JCV load at time of diagnosis

Foley J: Overview of clinical outcomes in cases of natalizumab-associated PML. (P15), CMSC, Montreal, 2011.
Vermersch P et al: Neurology 2011;76:1697-1704

Tysabri-treated PML Cases

Survival is Similar with or without PLEX/IA

Treatment Received (PLEX and/or IA)	Number (percent) survival
PLEX and/or IA	66/84, (79%)
NO PLEX or IA	4/4 (100%)
Unknown status	4/5 (80%)

BiogenIdec communication July 21, 2011
Data as of 28-Jan-2011

PML in the Monoclonal Era Efalizumab

Table I. Summary of post-marketing confirmed PML cases associated with efalizumab (n =3)

	Case 1	Case 2	Case 3
Origin of report	United States; safety registry*	United States; spontaneous report	Germany; spontaneous report
Age (y)/Sex	70/M	73/F	47/M
Efalizumab dose (weight)	90 mg weekly (96.8 kg)	50 mg weekly (56 kg)	125 mg weekly (unknown; "severely obese")
Indication	Psoriasis	Psoriasis	Psoriasis
Time on efalizumab therapy to event	~4 years	~3 years, 7 months	~3 years
Last dose of efalizumab	~3.5 weeks after initial presentation	~6 weeks after initial presentation	9-14 weeks after initial presentation
Outcome	Death ~7.5 weeks after initial presentation	Death ~2 months after initial presentation	Death ~6 months after initial presentation

*Post-marketing safety registry with approximately 1,429 patients treated with eflizumab as of December 2008.

Kothary N et al: J Am Acad Derm 2010;10.1016/j.jaad.2010.05.033

PML in the Monoclonal Era Rituximab

- RADAR (Research on Adverse Drug Event and Reports) project
- Review of PML cases with RTX from 1997-2008
- 52 LPD, 2 SLE, 1 RA, 1 IA pancytopenia, 1 ITP
- Concomitant Rxs included HSCT (7), purine analogues (26), alkylating agents (39)
- Median time from last RTX dose was 5.5 months
- Case fatality was 90%
- Median time to death was 2.0 months
- No consistent anti-PML Rx in survivors

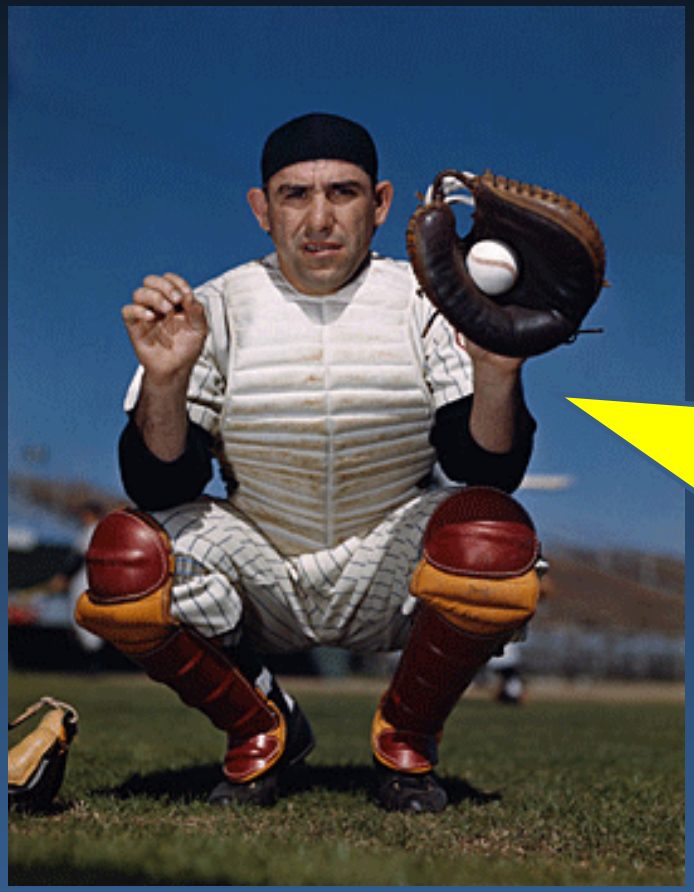
Carson KR et al: Blood, March 5, 2009, doi:10.1182/blood-2008-10-186999

Outcomes and PML Epochs

- Epoch
  - Pre-AIDS Epoch (1958-1981)
    - Virtually universally fatal
    - Rare outliers with long term survival
  - AIDS Epoch (1981-2005)
    - Pre-HAART similar to pre-AIDS epoch
    - Post-HAART long term survival approaches 50%
  - Monoclonal Epoch (2005 to present)
    - Natalizumab survival approximates 80%

Common Themes to Improved Outcome

- Outcome is, in large measure, predicted by the nature of the underlying immunological defect
  - Reversible or irreversible
- For PML due to reversible immunosuppression, i.e., monoclonal antibodies
  - Early detection of PML
  - Immediate removal of offending agent
- Future
  - Development of effective anti JC viral therapy
  - Remyelination



Yogi Berra
1925 - present

It's tough to make predictions, especially about the future.