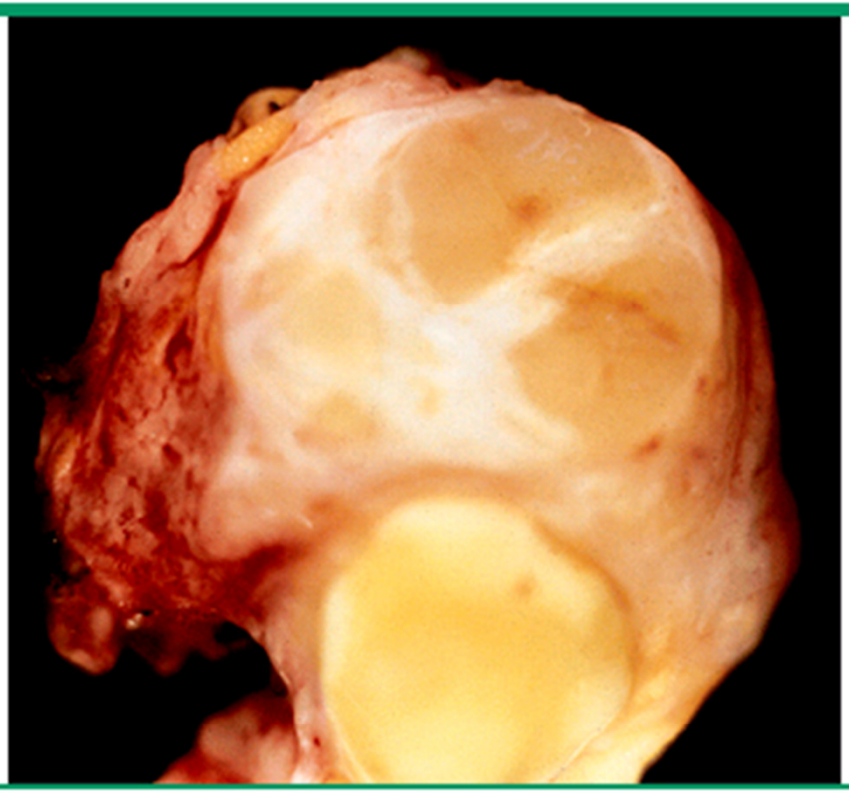
Case discussion

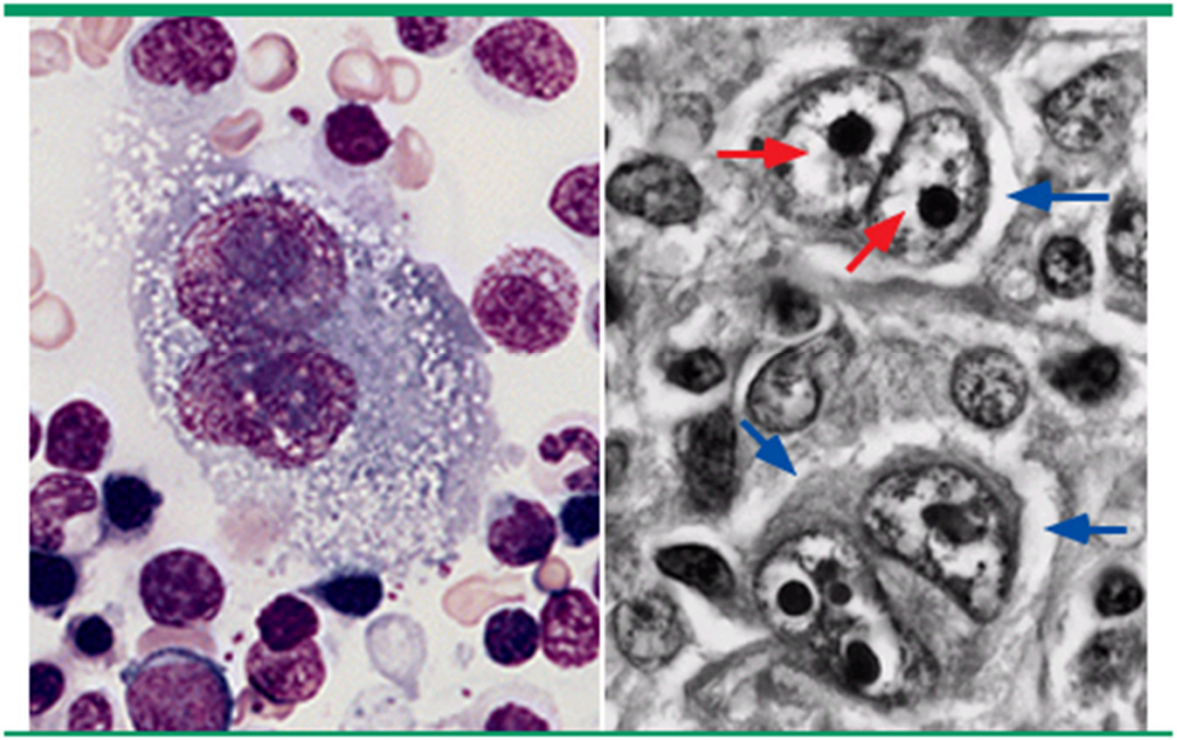
Lymph node in Hodgkin lymphoma



Cut section of a lymph node from a patient with the nodular sclerosis subtype of Hodgkin lymphoma shows distinct separation into nodules by fibrous bands.

From Warnke RA, Weiss LM, Chan JK, et al. Tumors of the lymph nodes and spleen. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 14, 1995, Washington, DC. Armed Forces Institute of Pathology.

Reed-Sternberg cells in Hodgkin lymphoma



Left panel: Reed-Sternberg cell as seen in a bone marrow specimen. Right panel: Reed-Sternberg cells in a lymph node section. Note the characteristic clear area surrounding the nucleoli in the right panel (red arrows), giving an "owl's eyes" appearance to the nuclei. Shrinkage artifact causes these cells to separate from the adjacent tissue, leaving a clear area surrounding these cells (ie, lacunar cells, blue arrows).

From Warnke, RA, Weiss, LM, Chan, JK, Cleary, ML, Dorfman, RF. Tumors of the lymph nodes and spleen. Atlas of tumor pathology (electronic fascicle), Third series, fascicle 14, 1995, Washington, DC. Armed Forces Institute of Pathology.

Pathology

- Microscopy: Sections from enalrged lymph node showing nodules associated with hyaline fibrosis. Within nodules and in other aggregates throughout node there is a pleomorphic population of lymphoid cells including Reed-Sternberg cells.
- Immunophenotyping: Abnormal cells are strongly CD30 +ve, show weak focal staining with CD15, CD45 –ve, strongly MUM1 +ve.
- Features typical of classical nodular sclerosing Hodgkin's lymphoma.

Antibodies, paraneoplastic syndromes and associated cancers

Antibody	Syndrome	Associated cancers
Well characterized paraneoplastic antibodies*		
Anti-Hu (ANNA-1)	Encephalomyelitis including cortical, limbic, brainstem encephalitis, cerebellar degeneration, myelitis, sensory neuronopathy, and/or autonomic dysfunction	SCLC, other
Anti-Yo (PCA-1)	Cerebellar degeneration	Gynecological, breast
Anti-Ri (ANNA-2)	Cerebellar degeneration, brainstem encephalitis, opsoclonus-myoclonus	Breast, gynecological, SCLC
Anti-Tr	Cerebellar degeneration	Hodgkin's lymphoma
Anti-CV2/CRMP5	Encephalomyelitis, cerebellar degeneration, chorea, peripheral neuropathy	SCLC, thymoma, other
Anti-Ma proteins• (Ma1, Ma2)	Limbic, hypothalamic, brainstem encephalitis (infrequently cerebellar degeneration)	Germ-cell tumors of testis, lung cancer, other solid tumors
Anti-amphiphysin	Stiff-person syndrome, encephalomyelitis	Breast, lung cancer
Anti-recoverinΔ	Cancer-associated retinopathy (CAR)	SCLC
Partially-characterized paraneoplastic antibodies*		
Anti-Zic 4	Cerebellar degeneration	SCLC
mGluR1	Cerebellar degeneration	No tumor or Hodgkin's lymphoma
ANNA-3	Sensory neuronopathy, encephalomyelitis	SCLC
PCA2	Encephalomyelitis, cerebellar degeneration	SCLC
Anti-bipolar cells of the retina	Melanoma-associated retinopathy (MAR)	Melanoma
Antibodies that occur with and without cancer association		
Anti-VGCC	Lambert-Eaton myasthenic syndrome, cerebellar dysfunction	SCLC
Anti-AChR	Myasthenia gravis	Thymoma
Anti-NMDAR	Multistage syndrome with memory and behavioral disturbances, psychosis, seizures, dyskinesias, and autonomic dysfunction	Teratoma
Anti-AMPAR	Limbic encephalitis, psychiatric disturbances	Variable solid tumors
Anti-GABA(B) receptor	Seizures, limbic encephalitis	SCLC
Anti-LGI1 (previously attributed to VGKC)	Limbic encephalitis, seizures	Thymoma, SCLC
Anti-CASPR2 (previously attributed to VGKC)	Morvan's syndrome and some patients with neuromyotonia	Thymoma and variable solid tumors
Anti-nAChR	Subacute pandysautonomia	SCLC, others
GlyR	Encephalomyelitis with muscle spasms, rigidity, myoclonus, hyperekplexia	Often without cancer

PCA: Purkinje cell antibody; ANNA: antineuronal-nuclear antibody; VGCC: voltage-gated calcium channel; VGKC: voltage-gated potassium channel; nAChR: neuronal acetyl-choline receptor.
* Well-characterized antibodies are those directed against antigens whose molecular identity is known, or that have been identified by several investigators. (Graus F, et al. J Neurol Neurosurg Psychiatry 2004; 75:1135.)
• Antibodies to Ma2: younger than 45 years, usually men with testicular germ-cell tumors; older than 45, men or women with lung cancer and less frequently other tumors. Ma1 antibodies often associated with tumors other than germ-cell neoplasms and confers a worse prognosis, with more prominent brainstem and cerebellar dysfunction.
Δ Other antibodies reported in a few or isolated cases include antibodies to tubby-like protein and the photoreceptor-specific nuclear receptor.

Paraneoplastics

- Western Blot: -ve for anti-Hu, -Yo, -Ri,-Ma1, -Ma2, -CV2/CRMP5, -amphiphisin

- BUT….

Paraneoplastics

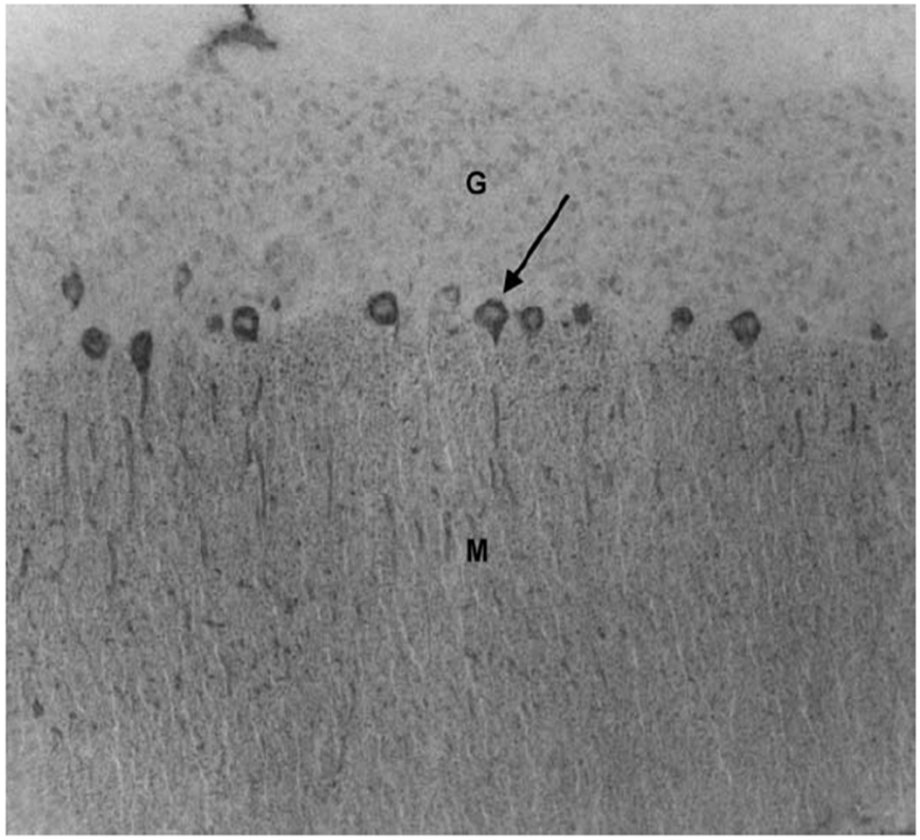


Figure 1. Frozen section of rat cerebellum incubated with biotinylated immunoglobulin G from anti-Tr positive patient's serum (dilution 1:6400) showing staining to cytoplasm and proximal dendrites of Purkinje cells (arrow) and punctate pattern of deposition in molecular layer (ICH, ×100 original magnification).

Treatment?

- Hickman line
- Doxorubicin, bleomycin, vinblastine, dacarbazide chemoRx
- Dex premed with chemo

- ?Should I give additional immunomodulatory treatment?

Treatment?

NICP

Treatment

Several single-case reports describe improvement in patients with PCD after treatment of the tumor, plasma exchange, intravenous immunoglobulin (IVIg), rituximab, or immunosuppression with cyclophosphamide or corticosteroids (Blaes et al., 1999; David et al., 1996; Shams'ili et al., 2006). However, most patients with PCD do not improve with any of these treatments (Vedeler et al., 2006).

Treatment?

TREATMENT

Definitive treatment is directed towards the underlying tumour; the neurological syndrome may then stabilise and even improve. There is evidence in anti-Hu associated encephalomyelitis that early cancer treatment improves neurological outcome.[13] Other syndromes in which tumour treatment is known to positively affect neurological outcome are: LEMS, myasthenia gravis, opsoclonus–myoclonus and stiff person syndrome. The Hodgkin's associated anti-Tr paraneoplastic cerebellar degeneration tends to improve with tumour therapy[14] whereas anti-Yo paraneoplastic cerebellar degeneration does not usually improve.[11]

In general, immune therapies such as corticosteroids, plasma exchange and intravenous immunoglobulin are more likely to affect neurological outcome when the syndrome is caused by an antibody directed against a cell surface antigen (N-methyl-d-aspartic acid (NMDA), voltage gated potassium channel (VGKC), voltage gated calcium channel (VGCC), acetylcholine receptor (AChR)). Fortunately, immune therapy does not appear to prejudice the oncological outcome.[15]

Pract Neurol 2010; 10: 260–270

Treatment?

Eur J Neurol. 2006 Jul;13(7):682-90.

Management of paraneoplastic neurological syndromes: report of an EFNS Task Force.

Vedeler CA, Antoine JC, Giometto B, Graus F, Grisold W, Hart IK, Honnorat J, Sillevis Smitt PA, Verschuuren JJ, Voltz R; Paraneoplastic Neurological Syndrome Euronetwork.

Department of Neurology, Haukeland University Hospital, Bergen, Norway. christian.vedeler@helse-bergen.no

Abstract

Paraneoplastic neurological syndromes (PNS) are remote effects of cancer on the nervous system. An overview of the management of classical PNS, i.e. paraneoplastic limbic encephalitis, subacute sensory neuronopathy, paraneoplastic cerebellar degeneration, paraneoplastic opsoclonus-myoclonus, Lambert-Eaton myasthenic syndrome and paraneoplastic peripheral nerve hyperexcitability is given. Myasthenia gravis and paraproteinemic neuropathies are not included in this report. No evidence-based recommendations were possible, but good practice points were agreed by consensus. Urgent investigation is indicated, especially in central nervous system (CNS) syndromes, to allow tumour therapy to be started early and prevent progressive neuronal death and irreversible disability. Onconeural antibodies are of great importance in the investigation of PNS and can be used to focus tumour search. PDG-PET is useful if the initial radiological tumour screen is negative. Early detection and treatment of the tumour is the approach that seems to offer the greatest chance for PNS stabilization. Immune therapy usually has no or modest effect on the CNS syndromes, whereas such therapy is beneficial for PNS affecting the neuromuscular junction. Symptomatic therapy should be offered to all patients with PNS.

Getting worse – what now?

- 09.11.10: “Dizzy”. Distal tingling. Lost ankle jerks. Vinblastine stopped.
- Repeat CT NCAP: Good response to chemoRx. (line tip atrial thrombus)
- ?Immunotherapy

High dose steroids and IVIg early on can be helpful. Worth trying if he is getting worse.

Dear David

This is a frequent question I get asked and my answer is uniformly No! The damage to the Purkinje cells is irreversible. If he regained some form of independent ambulation then he has

done well from this devastating condition.

Dr Jeremy Rees
Consultant Neurologist
National Hospital for Neurology and Neurosurgery

Queen Square

Treatment?

J Neurooncol (2007) 81:67–69
DOI 10.1007/s11060-006-9198-x

CLINICAL – PATIENT STUDIES

Neurologic improvement after high-dose intravenous immunoglobulin therapy in patients with paraneoplastic cerebellar degeneration associated with anti-Purkinje cell antibody

Surasak Phuphanich · Charles Brock

J Neurooncol (2008) 86:363–364
DOI 10.1007/s11060-007-9479-z

LETTER TO THE EDITOR

Successful treatment of paraneoplastic cerebellar degeneration with Rituximab

Marcello Esposito · P. Penza · G. Orefice · A. Pagano · E. Parente · A. Abbadessa · V. Bonavita

Treatment?

Leukemia & Lymphoma, September 2006; 47(9): 1960–1963

informa
healthcare

LETTER TO THE EDITOR

Paraneoplastic cerebellar degeneration associated with anti-neuronal anti-Tr antibodies in a patient with Hodgkin's disease

A. GEROMIN[1], A. CANDONI[1], G. MARCON[2], S. FERRARI[3], A. SPEROTTO[1], S. DE LUCA[1], & R. FANIN[1]

[1]*Division of Hematology and Bone Marrow Transplantation, Department of Medical and Morphological Research, University Hospital, Udine,* [2]*Division of Neuropathology and Neurology, Istituto Nazionale Neurologico C. Besta, Milano, and* [3]*Department of Clinical Neurology, University of Verona, Italy*

neuronal damage. Treatment with plasmapheresis and immunosopressive therapy has been reported, but improvement is transient and the results not encouraging; permanent improvement of neurologic symptoms has only rarely been reported [4]. The benefit of early high-dose intravenous prednisone is unclear; instead, early treatment with high doses of intravenous immunoglobulin (IVIG) with or without prednisone appears to provide a better chance of treatment success [10]. In several reports, anti-

Treatment?

10. Counsell CE, McLeod M, Grant R. Reversal of subacute paraneoplastic cerebellar syndrome with intravenous immunoglobulin. Neurology 1994;44:1144–1145.