

43rd ANNUAL DIAGNOSTIC SLIDE SESSION, 2002
REFERENCES AND DIAGNOSES

MODERATOR: E. Tessa Hedley-Whyte, M.D.
EDITOR: Leroy R. Sharer, M.D.

Case 2002-1

Submitted by: Saroja Ilangovan, M.D., Peter Pytel, M.D., Robert Wollman, M.D., Marc G. Reyes, M.D., and Rajeswari Chandran, M.D., Cook County Hospital and University of Chicago, Chicago, IL

Diagnosis: Dysferlin deficient myopathy

Comment: This patient had been treated at one point in her course with intravenous immunoglobulin (IVIG), with no effect. Immunocytochemical studies for sarcoglycans, dystrophin, and merosin were all normal. However, there was complete absence of dysferlin, which is also expressed in the sarcolemma at a point different from dystrophin. It was noted that there can be secondary loss of dysferlin from the muscle membranes, and the diagnosis needs to be confirmed by genetic analysis. The disorder is autosomal recessive, with the gene located at 2p13.

References:

Liu J et al.: Dysferlin, a novel skeletal muscle gene, is mutated in Miyoshi myopathy and limb girdle muscular dystrophy. *Nature Genetics* 1998; 20: 31-36.

Bushby KMD: Making sense of the limb girdle muscular dystrophies. *Brain* 1999; 122:1403-1420.

McNally EM et al.: Splicing mutations in Dysferlin produces limb-girdle muscular dystrophy with inflammation. *Am J Med Genet* 2000; 91:305-312.

Fanin M et al.: Calpain-3 and dysferlin protein screening in patient with limb girdle dystrophy and myopathy. *Neurology* 2001; 56:660-665.

Selcen D et al.: The earliest pathologic alterations in dysferlinopathy. *Neurology* 2001; 56:1472-1481.

Case 2002-2

Submitted by: Roberta J. Seidman, M.D., and Robert Greenwald, M.D., Stony Brook University Hospital, Stony Brook, NY, and Long Island Jewish Medical Center, New Hyde Park, NY

Diagnosis: Adult onset acid maltase deficiency

Comment: Vacuoles were PAS positive, with increased acid phosphatase activity as well. On electron microscopy (made available by Dr. Seidman after the presentation) membrane-

bound and free glycogen granules were increased within the muscle fibers. Cultured fibroblasts had 7% activity of acid alpha glucosidase activity. The mutation is linked to 17q25.2 -3. Ptosis is apparently an unusual finding in this disorder.

References:

Amalfitano A, Bengur AR, Morse RP, et al.: Recombinant human acid alpha-glucosidase enzyme therapy for infantile glycogen storage disease type II: results of a phase I/II clinical trial. *Genetics in Medicine* 2001; 3:132-8.

Carpenter S and Karpati G: Pathology of Skeletal Muscle, second edition, Oxford University Press, New York, 2001, pp. 487-492.

Rosenow EC and Engel AG: Acid maltase deficiency in adults presenting as respiratory failure: *Am J Med* 1978; 64:485-491.

Wokke JHJ, Ausems MGEM, van den Boogaard M-J H, et al.: Genotype-phenotype correlation in adult-onset acid maltase deficiency. *Ann Neurol* 1995; 38:450-454.

Case 2002-3

Submitted by: Antje Bornemann, M.D., Hans H Goebel, M.D., Jürgen Bohl, M.D., Romain Gherardi M.D., Departments of Neuropathology, Universities of Tübingen and Mainz, GERMANY, and Créteil/Paris, FRANCE

Diagnosis: Macrophagic myofasciitis

Comment: Electron micrographs of the macrophage infiltrates in the muscle revealed small spicules of electron dense material. On laser mass spectrum analysis, aluminum was found to be present. The patient had had a vaccination into the same upper extremity muscle some four weeks prior to the biopsy. This was a chance finding in this case, unrelated to the patient's neuromuscular disease. On genetic study, the patient was negative for the FSH dystrophy mutation.

References:

Gherardi RK, Coquet M, Chérin P, et al.: Macrophagic myofasciitis lesions assess long-term persistence of vaccine-derived aluminium hydroxide in muscle. *Brain* 2001; 124:1821-1831.

Mrak RE: Muscle granulomas following intramuscular injection. *Muscle Nerve* 1982; 5:637-639.

Case 2002-4

Submitted by: Angelica Oviedo, M.D., Ste. Justine Hospital, Montréal, Québec, CANADA

Diagnosis: Hereditary hemorrhagic telangiectasia, and systemic arterial dysplasia

Comment: Arteriogram during life demonstrated narrowing (stenosis) of the aorta, as well as renal artery stenosis, which clinically was associated with hypertension. These and other,

similar changes constituted lesions of systemic arterial dysplasia, which are shown on the submitted section of aorta, which has intimal thickening. The submitted slides from the brain and spinal cord, on the other hand, exhibit the vascular malformations of hereditary hemorrhagic telangiectasia.

Comment from the presenter: This case clearly demonstrates clinical and pathologic features of both hereditary hemorrhagic telangiectasia (HHT) and systemic arterial dysplasia (AD). HHT is autosomal dominant and has been linked to the endoglin gene on 9q3 and to the activin receptor-like kinase 1 gene on 12q11-q14. AD is also likely autosomal dominant; one patient has had a type III collagen mutation on 2q31. HHT and AD are considered non-overlapping syndromes. This is the first case which has features of both diseases.

References:

McAllister KA, Grogg KM, Johnson DW, et al.: Endoglin, a TGF-beta binding protein of endothelial cells, is the gene for hereditary haemorrhagic telangiectasia type. *Nat Genet* 1994; 8:345-51.

Kjeldsen AD, Brusgaard K, Poulsen L, et al.: Mutations in the ALK-1 gene and the phenotype of hereditary hemorrhagic telangiectasia in two large Danish families. *Am J Med Genet* 2001; 98:298-302.

Tromp G, Wu Y, Prockop DJ, et al.: Sequencing of cDNA from 50 unrelated patients reveals that mutations in the triple-helical domain of type III procollagen are an infrequent cause of aortic aneurysms. *J Clin Invest* 1993; 91:2539-45.

Case 2002-5

Submitted by: Dr. Samuel K. Ludwin, Queen's University, Kingston, Ontario, CANADA

Diagnosis: Grinker's myelinopathy

Comment: The patient, who had attempted to commit suicide by carbon monoxide (CO) inhalation, was treated with hyperbaric oxygen therapy. On gross inspection of the brain, there were discolorations in the hemispheric white matter, as well as lesions in the globus pallidus on each side. On microscopical examination there was acute neuronal necrosis in the globus pallidus, with focal white matter cavitation and diffuse hypomyelination, with axonal swellings and diffuse axonal loss. The changes in this case are indistinguishable from those seen with delayed hypoxic/ischemic leukoencephalopathy. They were first described by Grinker, who at the time was working in Jakob's laboratory.

References:

Okeda R, Song SY, Funta N, Higashino F: An experimental study of the pathogenesis of Grinker's myelinopathy in carbon monoxide intoxication. *Acta Neuropathol* 1983; 59:200-6.

Salama J, Gherardi R, Amiel H, Poirier J, Delaporte P, Gray F: Post-anoxic delayed encephalopathy with leukoencephalopathy and non-hemorrhagic cerebral amyloid angiopathy. *Clin Neuropathol* 1986; 5:153-6.

Horita N, Ando S, Seino S, Hagiwara I: Experimental carbon monoxide leucoencephalopathy in the cat. *J Neuropathol Exp Neurol* 1980; 39:197-211.

Case 2002-6

Submitted by: J.M. Bilbao, Sandra Black and Beverley Young, Sunnybrook and Women's College Health Sciences Centre, University of Toronto, Ontario, CANADA

Diagnosis: **Fronto-temporal dementia with ubiquitinated, tau-negative, neuronal inclusions (motor neuron disease type)**

Comment: The fronto-temporal changes included vacuoles in the upper cortical layers, with ubiquitin-positive inclusions in neurons. The hypoglossal nucleus had hyaline intranuclear inclusions, which were also ubiquitin positive. The spinal cord was not available for examination; the medullary pyramids were normal.

References:

Forno L, Langston JW, Herrick MK, Wilson JD, Murayama S: Ubiquitin positive neuronal and Tau 2-positive inclusions in FTD of motor neuron type. *Acta Neuropathol* 2002; 103:599-606.

Uchihara T, Sato T, Suzuki H, et al.: Bunina bodies in frontal lobe dementia without clinical manifestations of motor neuron disease. *Acta Neuropathol* 2001; 101:281-281.

Woulfe JM, Kertesz A, Munoz DG: Frontotemporal dementia with ubiquitinated cytoplasmic and intranuclear inclusions. *Acta Neuropathol* 2001; 102:94-102.

Case 2002-7

Submitted by: R.H. Laeng, M.D., Kantonsspital Aarau, Aarau, SWITZERLAND

Diagnosis: **Systemic autoimmune disease, consistent with systemic lupus erythematosus**, involving central and peripheral nervous systems, kidneys, liver, skin, and the hematopoietic system

Comment: The patient had antibodies to double-stranded (DS) DNA, consistent with a diagnosis of systemic lupus erythematosus (SLE). On FACS analysis, the cell infiltrates in the cerebellum were predominantly T cell in type, with CD4 cells outnumbering CD8 cells; no dominant T cell clone was found, ruling out a lymphoma. Biopsy of the skin lesions revealed lymphocytic dermatitis. Several alternative diagnoses were suggested by members of the audience, including hemophagocytic lymphocytic-histiocytic syndrome and paraneoplastic hemophagocytic syndrome. However, there was no evidence of hemophagocytosis in any of the tissues examined.

References:

Ellis SG, Verity MA: Central nervous system involvement in systemic lupus erythematosus: a review of neuropathologic findings in 57 cases, 1955-1977. *Semin Arthritis Rheum* 1979; 8:212-221.

Devinski O, Petito CK, Alonso DR: Clinical and neuropathological findings in systemic lupus erythematosus: the role of vasculitis, heart emboli and thrombotic thrombocytopenic purpura. *Ann Neurol* 1988; 23:380-384.

Hanly JG, Walsh NMG, Sangalang V: Brain pathology in systemic lupus erythematosus. *J Rheumatol* 1992; 19:732-741.

Schwartz MM, Fennel JS, Lewis EJ: Pathology of the renal tubule in systemic lupus erythematosus. *Hum Pathol* 1982; 13:534-547.

Case 2002-8

Submitted by: Margaret L. Grunnet, M.D., University of Connecticut Health Center, Farmington, CT

Diagnosis: Graft vs. host disease affecting the brain

Comment: There is a subacute panencephalitis in this case, mainly due to infiltration by CD3-positive cells. The appearance is more like an allergic than a paraneoplastic encephalitis. The audience was puzzled as to the precise diagnosis in this case.

References:

Padovan CS, Yousry TA, Schleuning M, Holler E, Kolb HJ, Straube A: Neurological and neuroradiological findings in long-term survivors of allogeneic bone marrow transplantation. *Ann Neurol* 1998; 43: 927-633.

Miura Y, Thoburn CJ, Bright EC, et al.: Characterization of the T-cell repertoire in autologous graft-versus-host disease (GVHD): evidence for the involvement of antigen-driven T-cell response in the development of autologous GVHD. *Blood* 2001; 98:868-879.

Hess AD and Thoburn CJ: Immunobiology and immunotherapeutic implications of syngeneic/autologous graft-versus-host disease. *Immunological Reviews* 1997; 157:111-123.

Case 2002-9

Submitted by: Eun-Sook Cho, M.D., and Leroy R. Sharer, M.D., UMD-New Jersey Medical School, Newark, NJ

Diagnosis: Extranodal, intracranial Rosai-Dorfman disease ("sinus histiocytosis with massive lymphadenopathy")

Comment: The large histocyte-like cells demonstrated emperipolesis (engulfment) of lymphocytes and plasma cells. The histiocyte-like cells on immunocytochemistry (ICC) were positive for S-100 protein and CD68, while they were negative for epithelial membrane antigen (EMA), CD1a, CD20, and CD30. It was noted that ICC for CD1a is not always

reliable in CNS specimens. Recent, in vitro data suggest that emperipolesis may be due to lymphocytic penetration into the large cells, rather than engulfment or phagocytosis.

References:

Rosai J: Sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman disease), in Rosai J, Ackerman's Surgical Pathology, eighth edition, Mosby, St. Louis, 1996, pp. 1694-1695.

Andriko JA, Morrison A, Colegial CH, Davis BJ, Jones RV: Rosai-Dorfman disease isolated to the central nervous system: a report of 11 cases. *Mod Pathol* 2001; 14:172-178.

Case 2002-10

Submitted by: Rafael Medina-Flores, M.D. and Ronald L. Hamilton, M.D., Presbyterian and Children's Hospital of Pittsburgh, University of Pittsburgh Medical Center, Pittsburgh, PA

Diagnosis: Atypical neurocytoma

Comment: The MIB-1 (Ki-67) labeling index was 15% at the first resection and even higher at the second. Electron microscopy revealed dense core vesicles. A microsatellite panel did not show loss of heterozygosity (LOH). Most observers thought that the tumor was a neurocytoma with large rosettes, while one observer favored a diagnosis of a differentiated embryonal tumor (or PNET) with advanced maturation along neurocytic lines.

References:

Mackenzie IR: Central neurocytoma: histologic atypia, proliferation potential and clinical outcome. *Cancer* 1999; 85:1606-10.

Favereaux A, Vital A, Loiseau H, Dousset V, Caille J, Petry K: Histopathological variants of central neurocytoma: report of 10 cases. *Ann Pathol* 2000; 20:558-63.

Vallat-Decouvelaere AV, Gauchez P, Varlet P, Delisle MB, Popovic M, Boissonnet H, Gigaud M, Mikol J, Hassoun J: So-called malignant and extra-ventricular neurocytomas: reality or wrong diagnosis? A critical review about two overdiagnosed cases. *J Neurooncol* 2000; 48:161-72.

Stapleton SR, David KM, Harkness WF, Harding BN: Central neurocytoma of the cervical spinal cord. *J Neurol Neurosurg Psychiatry* 1997; 63: 119.

Case 2002-11

Submitted by: Arie Perry, M.D., Washington University School of Medicine, St. Louis, MO

Diagnosis: Anaplastic oligodendroglioma with neurocytic differentiation

Comment: ICC for glial fibrillary acidic protein (GFAP) was positive in minigemistocyte-like or glial-fibrillary oligodendrocytes, while the small blue cells were negative for this antigen. ICC for NeuN was positive in the rosetted areas, while ICC for synaptophysin was equivocal. The

MIB-1 labeling index was 18% for the large cells, while there was no MIB-1 labeling of the small cells. Fluorescence in situ hybridization (FISH) was normal for 1p32 and 19q.

References:

Perry A, Scheithauer BW, Macaulay RJB, et al.: Oligodendrogliomas with neurocytic differentiation. A report of four cases with diagnostic and histogenetic implications. *J Neuropathol Exp Neurol* (in press).

Wharton SB, Chan KK, Hamilton FA, Anderson JR: Expression of neuronal markers in oligodendrogliomas: an immunohistochemical study. *Neuropathol Appl Neurobiol* 1998; 24:302-308.

Williams BP, Read J, Price J: The generation of neurons and oligodendrocytes from a common precursor cell. *Neuron* 1991; 7:685-693.