

**44th ANNUAL DIAGNOSTIC SLIDE SESSION, 2003
REFERENCES AND DIAGNOSES**

MODERATOR: E. Tessa Hedley-Whyte, M.D.

EDITOR: Leroy R. Sharer, M.D.

Case 2003-1

Submitted by: Fausto Rodriguez, M.D., Caterina Giannini, M.D., and Bernd Scheithauer, M.D., Mayo Clinic, Rochester, MN

Diagnosis: Solitary fibrous tumor and associated salivary gland heterotopia

Comment: The tumor was positive for CD34 and BCL2. The glandular component was positive for PAS and lysozyme, and the glands were surrounded by a layer of smooth muscle antigen (SMA) positive cells, indicating that the glands are benign.

References:

Carneiro SS, Scheithauer BW, Nascimento AG, et al.: Solitary fibrous tumor of the meninges: a lesion distinct from fibrous meningioma. A clinicopathologic and immunohistochemical study. *Am J Clin Pathol* 1996; 106:217-224.

Curry B, Taylor CW, Fisher AW: Salivary gland heterotopia: a unique cerebellopontine angle tumor. *Arch Pathol Lab Med* 1982; 106:35-38.

Peel R: Diseases of the salivary glands. In: Barnes L, *Surgical Pathology of the Head and Neck*, 2nd ed., New York, NY: Marcel Dekker Inc., 2001; pp. 647-649

Case 2003-2

Submitted by: William McDonald, M.D., and Andrew Bollen, D.V.M., M.D., UCSF, San Francisco, CA

Diagnosis: Paraganglioma with gangliocytic differentiation

Comment: Tumor cells were positive for chromogranin, according to a member of the audience. The presenter reported that the ganglionic tumor cells were positive for neurofilament protein, while the chief cells were positive for synaptophysin. The sustentacular cells were positive for S-100 protein.

The patient subsequently underwent hysterectomy for pelvic symptoms and four large leiomyomas were found. Neurological examination three months after her spinal canal tumor resection was normal, but the patient still had subjective complaints of pain and dysesthesia in her lower extremities.

Comment from the presenter: Paragangliomas are neural crest derived neoplasms that usually arise in association with autonomic ganglia. When arising within the adrenal medulla they are referred to as pheochromocytoma. They may arise in the setting of autosomal dominant syndromes including Multiple Endocrine Neoplasia type 2 (MEN2), von Hippel-Lindau disease (VHL), and rarely neurofibromatosis type 1 (NF1). One quarter of non-syndromic cases of pheochromocytoma and paraganglioma are, nevertheless, associated with germline mutations of RET, VHL, SDHD, and SDHB. The relationship between these mutations and paragangliomas arising in the cauda equina is currently unknown.

References:

Sonneland PR, Scheithauer BW, LeChago J, Crawford BG, Onofrio BM: Paraganglioma of the cauda equina region. Clinicopathologic study of 31 cases with special reference to immunocytology and ultrastructure. *Cancer* 1986; 58:1720-35.

Baysal BE. Hereditary paraganglioma targets diverse paraganglia. *J Med Genet* 2002; 39:617-22.

Neumann HP, et al, and the Freiburg-Warsaw-Columbus Pheochromocytoma Study Group: Germ-line mutations in nonsyndromic pheochromocytoma. *N Engl J Med* 2002; 346:1459-66.

Niemann S, Muller U: Mutations in SDHC cause autosomal dominant paraganglioma, type 3. *Nature Genetics* 2000; 26:268-70.

Case 2003-3

Submitted by: Ben Pang-Hsien Tu, Robert. E. Schmidt, and Arie Perry, Washington University, St. Louis, MO

Diagnosis: Extra-nodal marginal zone lymphoma (MALT) with tumefactive amyloid deposition

Comment: The cells were strongly positive for CD20, while the tumefactive areas stained for kappa light chain. The amyloid regions were strongly positive with thioflavin S staining. Only about 10 cases of this condition have been reported, all in middle-aged women.

References:

Goetz P, Lafuente J, Revesz T, et al.: Primary low-grade B-cell lymphoma of mucosa-associated lymphoid tissue of the dura mimicking the presentation of an acute subdural hematoma. Case report and review of the literature. *J Neurosurg* 2002; 96:611-614.

Lehman NL, Horoupian DS, Warnke RA, et al.: Dural marginal zone lymphoma with massive amyloid deposition: rare low-grade primary central nervous system B-cell lymphoma. Case report. *J Neurosurg* 2002; 96:368-72.

Kumar S, Kumar D, Kaldjian EP, Bauserman S, Raffeld M, Jaffe ES. Primary low-grade B-cell lymphoma of the dura. A mucosa associated lymphoid tissue-type lymphoma. *Am J Surg Pathol* 1997; 21:81-87.

Case 2003-4

Submitted by: France Berthelet, Notre-Dame Hospital, Montréal, Québec, CANADA

Diagnosis: Adult Alexander's disease with autosomal dominant transmission

Comment: CSF examination during life was normal. In the brainstem, there was cavitation of the pyramids, with general myelin pallor elsewhere. The white matter in many regions of the brain was pale, with astrogliosis and Rosenthal fibers. There were also Rosenthal fibers in the hypothalamus, in the cerebellar white matter (mainly in the hilus of the dentate nucleus), and in the gray and white matter of the spinal cord. There was neither inflammation nor evidence of macrophages in any of the sections.

Genetic testing of the patient's family has revealed a novel mutation in the first exon of the GFAP gene, in the rod domain of the protein. Five out of six heterozygotes in the family are symptomatic, with autosomal dominant transmission.

References:

Li R, Messing A, Goldman JE, Brenner M: GFAP mutations in Alexander's disease. *Int J Dev Neurosci* 2002; 20:259-268.

Brenner M, Johnson AB, Boespflug-Tanguy O, Rodriguez D, Goldman JE, Messing A: Mutations in GFAP, encoding glial fibrillary acidic protein are associated with Alexander's disease. *Nat Genet* 2001; 27:117-120.

Schawankhaus JD, Parisi JE, Gullledge WR, Chin L, Currier RD: Hereditary Alexander's disease with palatal myoclonus, spastic paraparesis, and cerebellar ataxia. *Neurology* 1995; 45:2266-2271.

Howard RS, Greenwood R, Gawler J, Scaravilli F, Marsden CD, Harding AE: A familial disorder associated with palatal myoclonus, other brainstem signs, tetraparesis, ataxia and Rosenthal fiber formation. J Neurol Neurosurg Psychiatry 1993; 56:977-981.

Case 2003-5

Submitted by: Rolf Pfannl, M.D., and E. Tessa Hedley-Whyte, M.D.,
Massachusetts General Hospital, Harvard Medical School, Boston, MA

Diagnosis: Bilateral degeneration of the amygdala of unknown etiology

Comment: On gross inspection, there was some temporal lobe atrophy on each side. The amygdalae were normal in size, with a bilateral central yellow-white nodule. The microscopic changes present on the slides that were sent out were identical in both amygdalae. One observer suggested grumous degeneration, similar to what can be seen in progressive supranuclear palsy. Dr. Kathy Newell reported that she had seen a similar case, with bilateral lesions in the amygdala, in a 40-year-old woman with non-familial, severe Alzheimer's disease. The current case also exhibited changes associated with Argyrophilic Grain Disease.

Comment from Dr. Hedley-Whyte: I am grateful to John Crary (MD/PhD student at SUNY Downstate, Brooklyn, NY) for bringing to our attention, subsequent to the meeting, an uncommon entity, Urbach-Wiethe's syndrome (lipoid proteinosis cutis et mucosae) This entity, amongst other things, is characterized by bilateral amygdala calcifications. The one or two autopsy reports of the brain have commented upon peculiar degenerative and vascular changes in the amygdalae. Whether our case truly represents this syndrome awaits further exploration.

References:

Holtz KH: Über Gehirn- und Augenveränderungen bei Hyalinosis cutis et mucosae (Lipoidproteinose) mit Autopsiebefund. Arch Klin Exp Derm 1962; 214:289-306.

Siebert M, Markowitsch HJ, Bartel P: Amygdala, affect and cognition: evidence from 10 patients with Urbach-Wiethe disease. Brain 2003 126: (advance electronic copy).

Newton FH, Rosenberg RN, Lampert PW, O'Brien JS: Neurologic involvement in Urbach-Wiethe's disease (lipoid proteinosis). A clinical, ultrastructural, and chemical study. Neurology 1971; 21:1205-1213.

Tolnay M, Ghebremedhin, Probst A, Braak H: Argyrophilic Grain Disease. In Neurodegeneration: The molecular pathology of Dementia and Movement Disorders, Dickson D, ed., ISN Neuropath Press, Basel 2003, pp.132-136.

Case 2003-6

Submitted by: Vernon Armbrustmacher, M. D., and Barbara A. Sampson, M.D., Ph.D., Office of the Chief Medical Examiner of the City of New York, New York, NY

Diagnosis: West Nile virus poliomyelitic encephalitis

Comment: This case occurred in the late summer. There was no evidence of hepatitis or myocarditis, at autopsy. PCR was positive for West Nile virus (WNV) in brain tissue, performed at the Centers for Disease Control and Prevention (CDC).

References:

Sampson BA, Njelds H, Armbrustmacher V, Asnis DS: Muscle weakness in West Nile encephalitis is due to destruction of motor neurons. Hum Pathol 2003; 34:628-629.

Sampson BA , Armbrustmacher V: West Nile encephalitis: the neuropathology of four fatalities. Ann N Y Acad Sci 2001; 951:172-178.

Sampson BA , Ambrosi C, Charlot A, Reiber K, Veress JF, Armbrustmacher V: The pathology of human West Nile Virus infection. Hum Pathol 2000; 31:527-531.

Case 2003-7

Submitted by: Ana Sotrel, M.D., William Bellini, Ph.D., Atilano G. Lacson, M.D., Mario A. Reyes, Nolan Altman, M.D., Jeannette Guarner, M.D., Glenn Morrison, M.D., and Michael Duchowny, M.D., Miami Children's Hospital and University of Miami, Miami, FL, Centers for Disease Control and Prevention, Atlanta, GA, and All Children's Hospital and University of South Florida, Tampa, FL

Diagnosis: Subacute sclerosing panencephalitis (SSPE)

Comment: From the presenter: SSPE is a rare, almost "forgotten," potentially "resurging" CNS disorder of children and young adults. It is a slowly-evolving, progressive, untreatable, viral/degenerative panencephalopathy with or without retinopathy, caused by a persistent CNS-retinal infection with a defective, hypermutated, SSPE-form of wild measles virus (WMV). SSPE usually starts

~9y after either a clinically apparent or a subclinical form of systemic WMV infection. No vaccine strains of measles virus have been documented as the cause, by genomic sequence analysis (GSA) in SSPE patients, even though 50% of them have had a history of measles vaccination. Their SSPE is most likely related to a presumed or known exposure to WMV before vaccination took place, at <1y of age. From 1989-1991 there was resurgence of measles in the USA, well documented in 55,622 children, most of whom were either unvaccinated and less than 5 years of age, or pre-vaccinated at greater than 1 year of age. Most causative WMVs during this epidemic were shown to belong to a single indigenous MV-genotype D3.

This patient was born in the USA in 1990 (during the period of the epidemic), and she was first vaccinated in 1991. The light and electron microscopic diagnosis of SSPE was confirmed by the CDC by the demonstration of CSF titers of MV-specific IgG (1:6,400), as well as by immunohistochemically demonstrable MV-antigen within the paraffin-embedded brain tissue, in glial and neuronal nuclei. MV RNA was detected in frozen brain tissue and was proven to be WMV-genotype D3 by GSA (as opposed to the MV-genotype A, which is contained in all currently used measles vaccines).

References:

Garg RK. Subacute sclerosing panencephalitis (review). *Postgrad Med J* 2002; 78:63-70.

Griffin D, Bellini W: Measles virus. In: *Field's Virology*, Field BN, et al., eds., Philadelphia-New York: Lippincott-Raven, 1996, pp. 1267-1312.

Mgone CS et al. Clinical presentation of subacute sclerosing panencephalitis in Papua New Guinea. *Tropical Medicine and International Health* 2003; 8:219-227.

Orenstein WA, Strebel PM, Papania M, Sutter RW, Bellini WJ, and Cochi SL. Measles eradication: Is it in our future? *Am J Pub Health* 2000; 90:1521-1525.

Case 2003-8

Submitted by: Joshua D. Stephany, M.D., and Gary S. Pearl, M.D., Ph.D., Orlando Regional Medical Center, Orlando, FL

Diagnosis: Amebic meningoencephalitis consistent with *Naegleria fowleri*

Comment: This type of meningoencephalitis was first reported from Orlando, Florida, in 1966. A member of the audience pointed out that the organisms can be recognized in cerebrospinal fluid. The treatment of choice for this disease is amphotericin.

References:

Butt CG: Primary amebic meningoencephalitis. N Engl J Med 1966; 274:1473-1476.

Ma P, Visvesvara G, Martinez A, Theodore F, et al: Naegleria and Acanthamoeba infections: Review. Rev Infect Dis 1990; 12:490-513.

Marciano-Cabral F: Biology of Naegleria spp. Microbiol Rev 1988; 52:114-133.

Case 2003-9

Submitted by: Edward S. Johnson, M.D., Kinga Kowaleswska-Grochowska, M.D., Stan Houston, M.D., and John McKean, M.B.,Ch.B., University of Alberta, Edmonton, Alberta, CANADA

Diagnosis: Focal cerebral neuro-schistosomiasis due to *Schistosoma mekongi*

Comment: In addition to the history supplied, after the lesion was excised it was learned that the patient had recently traveled to Laos, where he swam in the Mekong River on several occasions. The history of travel to the Carribean proved to be incorrect. The diagnosis in this case was made on examination of organisms recovered at the time of surgery. *S. mekongi* does not have a lateral spine, in contrast with *S. mansoni*. The patient had serology that was positive for both *S. japonica* and *S. mekongi*.

References:

Gjerde IO, et al.: Cerebral schistosomiasis presenting as a brain tumor. Eur Neurol 1984; 23:229-236.

MacKenzie IAR, Guha A: Manson's schistosomiasis presenting as a brain tumor. J Neurosurg 1998; 89:1052-1054.

Pittella JEH: Neuroschistosomiasis. Brain Path 1997; 7:649-662.

Urbani C, et al.: Epidemiology and control of mekongi schistosomiasis. Acta Tropica 2002; 82:157-168.

Editor's note: Dr. Carlo Urbani, an expert in parasitic diseases with the World Health Organization, was one of the first people to recognize the newly emerging infection, severe acute respiratory syndrome, or SARS, which he described in Hanoi, Vietnam (reference: Ksiazek TG, Urbani C, and the SARS Working Group: A novel coronavirus associated with severe acute respiratory syndrome. N Engl J Med 2003; 348:1953-1966). Dr. Urbani died of SARS in March 2003.

Case 2003-10

Submitted by: Roberta J. Seidman, M.D., and Stephanie Horowitz, M.D., Stony Brook University Hospital, Stony Brook, NY, and Office of the Medical Examiner, Suffolk County, NY

Diagnosis: Adrenoleukodystrophy, adult cerebral type

Comment: There was some loss of axons, in severely involved areas, as judged by immunocytochemistry for neurofilament protein. Electron microscopy revealed lamellar or striated inclusions in macrophages. The adrenals were not atrophic, but the adrenal cortical cells were distended with material that had striated inclusions, on EM. The peripheral nerve was normal. ALD is a peroxisomal disorder, with a mutation at Xq28. The ALD protein is a peroxisomal membrane protein.

References:

Moser HW, Bezman L, Lu SE, Raymond GV: Therapy of X-linked adrenoleukodystrophy: prognosis based upon age and MRI abnormality and plans for placebo-controlled trials. *J Inher Metabolic Dis* 2000; 23:273-277.

Powers JM: Adreno-leukodystrophy (adreno-testiculo-leukomyelo-neuropathic-complex). *Clin Neuropathol* 1985; 4:181-199.

Powers JM: The pathology of peroxisomal disorders with pathogenetic considerations. *J Neuropathol Exp Neurol* 1995; 54:710-719.

Powers JM: Normal and defective neuronal membranes: structure and function: neuronal lesions in peroxisomal disorders. *J Mol Neurosci* 2001; 16:285-287; discussion 317-321.

Powers JM, Liu Y, Moser AB, Moser HW: The inflammatory myelinopathy of adreno-leukodystrophy: cells, effector molecules, and pathogenetic implications. *J Neuropathol Exp Neurol* 1992; 51:630-643.