MAYO CLINIC

Mayo Clinic
Neuropathology Laboratory
Birdsall Medical Research Building
4500 San Pablo Road
Jacksonville, Florida 32224
(904) 953-7137

December 1, 2023

Mr. Dag Forssell
2140 Santa Cruz Avenue, Apartment C 204
Menlo Park, CA 94025

Dear Mr. Forssell,

Enclosed please find a copy of the neuropathology report on your late wife Christine. After reviewing the tissue, there are several distinct disease processes. The major disorder is Lewy body disease with neuronal pathology most marked in limbic areas and associated with neuronal loss in the ventrolateral cell group of the substantia nigra. This is consistent with your wife's Parkinson's disease, which fits with her clinical diagnosis of Parkinson's disease. Considering the distribution and density of cortical Lewy bodies and the minimal Alzheimer type pathology the likelihood that she would have had clinical features of LBD is high. The medical records document she had Parkinsonism, but only mild cognitive impairment and no documentation of fluctuations, sleep disorder, or psychiatric features.

There were also multiple cerebral cortical metastases of malignant melanoma. Christine had a history of melanoma in her right arm, and she had wide local excision in 2021. There is suggestion from epidemiologic studies that melanoma may be more frequent in Parkinson's disease.

Finally, there were mild age-related changes, including mild medial temporal neurofibrillary tangles consistent with primary age-related tauopathy (PART), a finding of unclear clinical significance. She also had amyloid angiopathy, as well as arteriosclerotic small vessel pathology and large vessel atherosclerotic disease, with ischemic white matter changes and cribriform changes in deep gray matter. The tissue has been saved and will be used for experimental research on Lewy body dementia. Please feel free to share these findings with the treating physician.

I would like to extend our condolences to you along with our appreciation for allowing us to study tissue from your wife. It is only through the generous donation of tissue from loved ones, often at very difficult times, by individuals such as yourself that we are able to make any progress in research towards better understanding what causes, as well as how we may one day better diagnose, treat, and prevent disorders of this nature.

If I can be of any further assistance, please do not hesitate to contact me.

Sincerely,

Dennis W. Dickson, M.D.
Neuropathology Consultant

Enc. DWD/RLH

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November 29, 2023

Clara Lusardi, Pathology Specialist
901 Bayshore Boulevard - Suite 403
San Francisco, CA 94124-2290

Re: FORSSELL, CHRISTINE
Our: NA23-374

NEUROPATHOLOGY GROSS DESCRIPTION:

The fixed left hemibrain weighs 580 grams, and the calculated whole brain weight is 1160 grams. The cerebral hemisphere has normal configuration. The dorsal leptomeninges are clear, but there are several nodular foci of red-black discoloration in medial and lateral frontal lobe. The sulci and gyri reveal no cortical atrophy over the convexity or the medial temporal lobe. There are no areas of discoloration or softening. There is no cingulate herniation. The leptomeninges over the base of the brain are translucent. The available blood vessels at the base of the brain show a normal adult configuration of the circle of Willis and extensive atherosclerosis that produces multiple segments of 50% or greater stenosis. There is no uncal herniation. The infratentorial tissues are externally unremarkable. The leptomeninges are clear. There are no areas of discoloration or softening. There are no significant herniations.

Sequential sections through the supratentorial tissues reveal the ventricular system to be uncompressed, undilated and undisplaced, except for mild rounding of the frontal horn. The cortical gray mantle is normal in thickness and distribution. The hippocampal formation and amygdala are unremarkable. The subjacent white matter shows no unusual features. The basal ganglia are notable for foci of red-gray discoloration in the internal capsule, lateral caudate nucleus and ventral putamen caudate. The thalamus and subthalamic nucleus are unremarkable. The aqueduct of Sylvius is patent. Horizontal sections of the midbrain, pons and medulla at right angles to the neuraxis are unremarkable. The substantia nigra and the locus ceruleus have dark pigmentation. The cerebellar sections show no unusual features.

DWD
11/9/23

NEUROPATHOLOGY MICROSCOPIC DESCRIPTION:

Sections of the neocortex (x6), hippocampus (x2), basal forebrain, basal ganglia, thalamus, midbrain, pons, medulla and cerebellum (x2) are examined with H&E. Sections of the neocortex (x5), hippocampus, basal forebrain, basal ganglia and cerebellum are studied with thioflavin-S fluorescent microscopy. Sections of cortex, hippocampus and basal forebrain, as well as brainstem, are studied with immunocytochemistry for α-synuclein. A section of cortex that has samples from several of the focal lesions noted on gross examination is processed for S-100 and HMB-45 immunohistochemistry. The findings are consistent with metastatic melanoma (positive on S-100 and HMB-45).

The neocortex is unremarkable, except for multiple highly vascular lesions with small pigment-laden atypical cells consistent with metastatic melanoma. There is no subjective neuronal loss or gliosis. With thioflavin-S fluorescent microscopy no senile plaques (SP) or neurofibrillary tangles (NFT) are detected, but there is mild amyloid angiopathy in parenchymal and leptomeningeal vessels. There is also pervasive arteriosclerotic small vessel pathology, with cribriform change. The cerebral white matter has myelinated fiber loss and perivenous collagenosis in the periventricular region. The lesion counts in cortical sections with thioflavin S fluorescent microscopy are as follows:

	Senile plaques (per 10x field)	Neurofibrillary tangles (per 40x field)	Amyloid angiopathy
Mid-frontal	0	0	0-1+
Superior temporal	0	0	0-1+
Inferior parietal	0	0	1+
Motor cortex	0	0	1+
Visual cortex	0	0	1+

The hippocampus has a normal neuronal population in all sectors of Ammon's horn. There are only a few NFT in Sommer's sector. No Hirano bodies or granulovacuolar degeneration is detected. No SP are present in pyramidal layer or the molecular layer of the dentate fascia. No NFT are detected in the dentate fascia. Sparse dystrophic neurites are detected in the CA2/3 region with α-synuclein immunocytochemistry. The lesion counts in the hippocampal sectors with thioflavin S fluorescent microscopy are as follows:

	Senile plaques (per 10x field)	Neurofibrillary tangles (per 40x field)
Endplate	0	0
CA2/3	0	0-1
CA1	0	0-1
Subiculum	0	0

The entorhinal cortex has no SP (0 per 10x field) and only a few NFT in layer II (0-1 per 40x field) and in lower cortical layers (0-1 per 40x field). The Braak neurofibrillary tangle stage is consistent with Stage III.

There are cytoplasmic inclusions consistent with cortical Lewy bodies in most cortices, but they are most numerous in limbic and paralimbic cortices, including the parahippocampal cortex and the cingulate gyrus with α-synuclein immunohistochemistry. There are sparse Lewy neurites. The number of lesions per region is as follows:

Cortical Region	Lewy bodies (per 20x field)
Mid-frontal	0-1
Superior temporal	1-5
Inferior parietal	0
Cingulate gyrus	3-5
Parahippocampal gyrus	1-3

The basal nucleus of Meynert has neuronal depopulation, but no NFT (0 per 40x field) are detected with thioflavin S fluorescent microscopy. On the other hand, Lewy bodies and Lewy neurites are frequent in the basal forebrain. The hypothalamus also has Lewy bodies, but no SP or NFT. No SP or NFT are detected in the amygdala with thioflavin S fluorescent microscopy (corticomedial: 0 SP per 10x field and 0 NFT per 40x field; basolateral: 0 SP per 10x field and 0 NFT per 40x field). There are many Lewy bodies and Lewy neurites in the amygdala, especially in the cortical transition zone (20-25 per 20x field). The basal ganglia are unremarkable except for cribriform change in the striatum and mild calcific vasculopathy in the globus pallidus. Immunohistochemistry for α-synuclein immunostain shows sparse neurites in putamen and moderate axonal spheroids in the globus pallidus. There are no SP or NFT in the striatum with thioflavin S fluorescent microscopy. The thalamus and subthalamic nucleus are unremarkable.

The substantia nigra has moderate neuronal loss with extraneuronal neuromelanin and Lewy bodies in residual neurons. The neuronal loss is patchy, but most marked in the ventrolateral cell group. There is also small vessel pathology and cribriform change. Lewy bodies are also present in the raphe nuclei and periaqueductal gray matter. The locus ceruleus has neuronal loss and gliosis with many Lewy bodies and Lewy neurites. The lower brainstem and brainstem fiber tracts are remarkable for Lewy bodies and Lewy neurites in the dorsal motor nucleus of the vagus. The cerebellum shows well preserved Purkinje and internal granular cell layers, with only minimal focal Bergmann gliosis. No amyloid deposits or amyloid angiopathy are present in the cerebellum.

NEUROPATHOLOGY DIAGNOSES:

1. TRANSITIONAL (LIMBIC) LEWY BODY DISEASE
2. METASTATIC MELANOMA
3. PRIMARY AGE-RELATED TAUOPATHY (BRAAK STAGE II-III)
4. AMYLOID ANGIOPATHY
5. ATHEROSCLEROTIC AND ARTERIOSCLEROTIC VASCULAR DISEASE
6. LEUKOARAIOSIS
7. CRIBRIFORM CHANGE, BASAL GANGLIA AND THALAMUS

COMMENT:

There are several distinct disease processes. The major disorder is Lewy body disease with neuronal pathology most marked in limbic areas and associated with neuronal loss in the ventrolateral cell group of the substantia nigra. These findings are consistent with Parkinson's disease [1], which fits with her clinical diagnosis of Parkinson's disease. Considering the distribution and density of cortical Lewy bodies and the minimal Alzheimer type pathology, the likelihood that she would have had clinical features Lewy body dementia is high [2]. The available clinical information indicates she had Parkinsonism, but only mild cognitive impairment and no documentation of fluctuations, sleep disorder or psychiatric features (e.g., visual hallucinations).

There were also multiple cerebral cortical metastases of malignant melanoma. She had a history of melanoma of her right arm, and she had wide local excision 2-years before she died. There is suggestion from epidemiologic studies that melanoma may be more frequent in Parkinson's disease, but the mechanism remains unclear [3].

There were also mild age-related changes, including mild medial temporal neurofibrillary tangles consistent with primary age-related tauopathy (PART) [4], a finding of unclear clinical significance. She also had amyloid angiopathy, as well as arteriosclerotic small vessel pathology

and large vessel atherosclerotic disease, with ischemic white matter changes (leukoaraiosis) and cribriform change in deep gray matter (basal ganglia and thalamus).

References:

1. Dickson DW, Braak H, Duda JE, et al. Neuropathological assessment of Parkinson's disease: refining the diagnostic criteria. *Lancet Neurol* 2009;8:1150-1157.
2. McKeith IG, Boeve BF, Dickson DW, et al. Diagnosis and management of dementia with Lewy bodies: Fourth consensus report of the DLB Consortium. *Neurology* 2017;89:88-100.
3. Bose A, Petsko GA, Eliezer D. Parkinson's disease and melanoma: co-occurrence and mechanisms. *J Parkinsons Dis* 2018;8:385-398.
4. Crary JF, Trojanowski JQ, Schneider JA, et al. Primary age-related tauopathy (PART): a common pathology associated with human aging. *Acta Neuropathol* 2014;128:755-766.

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11/29/23