COLLEGE of AMERICAN PATHOLOGISTS

Autopsy Committee Sample Autopsy Case

Alzheimer Disease

Authors
Ashley Thorburn, MD

Joseph E. Parisi, MD
Autopsy Committee

Clinical Summary:
A 75-year-old man presented to his primary care physician with a three-day history of fever and chest pain. He had a history of progressive memory loss, as reported by his wife and daughter, but no other complaints. His past medical history included medically managed hypertension and hyperlipidemia. He lived at home with his wife and had 3 children in the area. He had a remote 4 pack-year smoking history and denied alcohol use. On physical examination, he was tachypneic with an oxygen saturation of 92% on room air. Chest x-ray revealed consolidation of the left lobe, and he was admitted to the hospital. Despite aggressive therapy, including antibiotics, he died.

Autopsy Findings:
At autopsy, the patient weighed 130 pounds and measured 5'10" (BMI = 18.7). His lungs had a combined weight of 1300 grams (expected: 1100 grams). The heart showed mild left ventricular hypertrophy. The brain weighed 1000 grams and showed mild generalized atrophy that was most prominent in medial temporal areas.

Questions and Discussion: (correct response is underlined)

1. The pulmonary findings and clinical picture in this case are most consistent with:	**Respondents**	
	No.	**%**
Bronchopneumonia secondary to aspiration	347	91.6
Lobar pneumonia secondary to aspiration	29	7.7
Desquamative interstitial pneumonia	2	0.5
Bronchiolitis obliterans organizing pneumonia	1	0.3
Bronchioloalveolar carcinoma	-	-

The immediate cause of death in most patients with dementia is pneumonia. Other commonly encountered causes of death in dementia patients include heart disease, sepsis, pulmonary thromboembolism, and cancer. A study of 52 autopsied patients with dementia from the UCLA Alzheimer Disease Research Center from 1995-2000 found that approximately 46% of patients had pneumonia as a primary cause of death. Pneumonia has been named as the most common cause of death in the general geriatric population, as well. This trend in cause of death in the elderly and bedridden patients is likely due to the inability to effectively clear respiratory secretions, compounded by a compromised immune system.[1]

Bronchopneumonia is characterized by multifocal consolidation in at least one pulmonary lobe. It may be caused by a variety of bacterial organisms, including, but not limited to, *Staphylococcus aureus, Klebsiella pneumoniae, Streptococcus sp.,* and *Escherichia coli*. The choice of empiric treatment for pneumonia depends upon several factors including the nature of the pneumonia, whether it is community-acquired or hospital-acquired, and whether the patient will be treated as an outpatient or inpatient. Uncomplicated outpatient empiric coverage for pneumonia is typically a macrolide such as azithromycin, along with doxycycline. In hospitalized patients, empiric treatment is centered upon the use of a third generation cephalosporin or respiratory fluoroquinolone such as levofloxacin. Vital signs are important to monitor in patients with bronchopneumonia, specifically looking for changes in respiratory rate, temperature, and peripheral oxygen saturation. A chest x-ray is essential for visualization of the extent of pulmonary involvement. Refractory pneumonia, particularly in the elderly or immunocompromised patient, can lead to death. At autopsy, the lungs are heavy with fluid collection and consolidation. On microscopic examination, the affected pulmonary regions show acute inflammation as in this case, and sometimes microabscesses.[2]

Lobar pneumonia secondary to aspiration is not an uncommon progression from bronchopneumonia, but is becoming less common due to rapid medical intervention. Lobar pneumonia appears as consolidation at autopsy, involving an entire pulmonary lobe. The chest x-ray in this case did not show full lobe involvement. Bronchiolitis obliterans organizing pneumonia is less common and characterized histologically by involvement of the alveolar spaces, alveolar ducts, and small bronchioles with fibroblast plugs with variable plasma cells and lymphocytes. Desquamative interstitial pneumonia falls within the group of idiopathic interstitial pneumonias and is characterized by the presence of chronic inflammation with or without fibrosis within interstitial spaces.[3] Bronchioloalveolar carcinoma is identified histologically by the presence of neoplastic cells forming masses greater than 5 mm and may be mucinous.[4]

2. The gross neuropathological findings suggest which diagnosis?	**Respondents**	
	No.	**%**
Alzheimer disease	370	97.9
Frontotemporal lobar degeneration	4	1.1
Lewy body disease	2	0.5
Creutzfeldt-Jakob disease	1	0.3
Multi-infarct dementia	1	0.3

3. Which of the following is a characteristic histological lesion of this disorder?	**Respondents**	
	No.	**%**
Neuofibrillary tangle	374	98.7
Astrocytic plaque	3	0.8
Lewy body	2	0.5
Glial cytoplasmic inclusion	-	-
Pick body	-	-

4. Which immunostain(s) highlights the characteristic histological lesions of this disorder?	Respondents No.	%
β-amyloid and tau	378	99.7
α-synuclein	1	0.3
GFAP	-	-
NSE	-	-
TDP-43	-	-

Alzheimer disease (AD) is the most common cause of dementia in the elderly. It is estimated that approximately 4.9 million people over the age of 65 carry the diagnosis of AD.[5] The disease is a great burden to families and society and has significant implications for Medicare/Medicaid. Although advances in providing premortem clinical, radiographic, and biomarker evidence of the disease have been made, the definitive diagnosis of AD is made by tissue examination of brain at biopsy or at autopsy.

Gross examination of the AD brain at autopsy reveals generalized (nonlobar) cerebral atrophy that is most prominent in medial temporal areas. In this case, mild generalized cerebral atrophy is evidenced at the surface by widened cortical sulci and narrowed gyri. On section, there is moderate ventricular enlargement with “blunt” (not sharp) angles of the lateral ventricle (arrows) and moderate to marked enlargement of the temporal horns secondary to atrophy of adjacent medial temporal structures (dotted areas).

Histologically, a spectrum of lesions is present. The cardinal lesions include senile plaques composed of extracellular deposits of Aβ (amyloid-beta) and neurofibrillary tangles composed of intraneuronal aggregates of tau.[6] The lesions of AD classically have been defined by silver stains but more recently are highlighted by immunostains to Aβ and tau. In a typical case, the diagnosis is suggested at low power: the neocortex is flooded with an abundance of silver-positive and Aβ-immunoreactive plaques.

The extracellular Aβ deposits (senile plaques) occur as either non-compact "diffuse plaques” (DPs) or "cored plaques." With modified Bielschowsky silver, DPs appear as vague areas of increased staining without neurites, while neuritic plaques (NPs) have associated dystrophic neurites that impart a “tumbleweed” appearance to the lesions. Aβ-immunostains do not reliably distinguish DPs from NPs since both are characterized by amyloid, but do demonstrate plaques of noncompact amyloid, and plaques with dense amyloid cores.

Cerebral amyloid angiopathy also typically is present in AD and can be highlighted with the Aβ-immunostain.

Neurofibrillary lesions include neuropil threads and intracellular neurofibrillary tangles (NFTs) composed of aggregates of hyperphosphorylated tau.[6] These lesions are well demonstrated with silver stains and especially with antibodies to tau. Tau also accumulates in the dystrophic neurites that comprise the neuritic plaques, as well as in threads and pretangles (granular intracytoplasmic neuronal deposits, presumed precursors of mature tangles).

Neurofibrillary pathology progresses in a predictable hierarchical order of involvement that begins in medial temporal (limbic) areas (entorhinal cortex to hippocampus) and then advances to association cortices and, finally, to primary sensory cortices. This progression is the basis of the Braak and Braak staging of the severity of AD,[7] correlates with the degree of clinical disability, and is a component of the current NIA-Reagan criteria for the pathological diagnosis of AD.[8] Since both tau and β-amyloid lesions characterize the pathologic lesions in this disorder, AD is considered both a tauopathy and β-amyloidopathy.

An essential feature of AD is the accumulation of Aβ peptides, derived from amyloid β precursor protein (AßPP).[9] A considerable body of work supports the deposition of Aß as the primary event in the pathogenesis of AD. Failure of degradation or clearance of Aß underlies its accumulation. It is important for the pathologist to distinguish non-compact amyloid deposits (DPs) from NPs. As detailed above, DPs lack dystrophic neurites and do not carry the same clinical significance as NPs. Although DPs may be considered a precursor stage of the NP, this is not always the case.[10]

Lewy body disease (LBD) includes a spectrum of disorders defined by the presence of α-synuclein-immunoreactive Lewy bodies and neuritis; in the prototypical Parkinson disease, now recognized as the brainstem variant of LBD, these lesions are confined to the brainstem.[11] This family of disorders typically does not present with atrophy of the medial temporal lobes. Multi-infarct dementia, in its pure form, is an uncommon cause of dementia. As its name implies, multi-infarct dementia is characterized by the presence of numerous infarcts with significant tissue destruction.[12] Frontotemporal lobar degeneration (FTLD), as its name implies, is characterized grossly by severe lobar atrophy that involves the frontal lobe, the temporal lobe, or both; many but not all FTLDs demonstrate TDP-43- or tau-immunoreactive lesions. Creutzfeldt-Jakob disease is a prion disorder usually characterized clinically by a rapidly progressive dementia with myoclonus and microscopically by spongiform change.[13]

5. Which of the following brain regions is most vulnerable to the pathologic lesions in this disorder?	**Respondents**	
	No.	**%**
Entorhinal cortex	368	97.4
Paraventricular nucleus	4	1.1
Hypothalamus	3	0.8
Mammillary bodies	3	0.8
Cerebellum	-	-

As described above, medial temporal structures, particularly entorhinal cortex, amygdala, hippocampus, and subiculum are the most vulnerable areas in AD. Various radiographic measurement techniques have been attempted for the early non-invasive diagnosis of AD. Hippocampal atrophy can be diagnosed by measuring the hippocampal sulcus width on T1-weighted MR imaging.[14] Patients with AD have been distinguished from age-matched controls by a significant bilateral reduction in blood flow or metabolism in the temporoparietal cortex using functional neuroimaging.[15] Additionally, perfusion and diffusion-weighted MR imaging illustrate a bilateral reduction in perfusion in the sensorimotor regions in patients with AD. The radiographic evidence of hypoperfusion in these regions correlates with the early and prominent neuropathological involvement of medial temporal structures and clinical impairment of recent memory.

6. A presumptive diagnosis of this disorder may be supported by an increase in the cerebrospinal fluid of which of the following biomarkers?	Respondents No.	%
tau	354	93.7
Amyloid precursor protein-alpha	14	3.7
β-amyloid	9	2.4
α-synuclein	1	0.3

In recent years, many studies have focused upon the identification of potential biomarkers of AD that would permit earlier diagnosis and potential therapies. Neuroimaging techniques hold considerable promise since they permit in vivo MRI measurement of hippocampal volume, cerebral activity by positron emission tomography (PET), and an estimation of Aβ plaque burden with Pittsburgh Compound-B (PIB). Clinical levels of cerebrospinal fluid (CSF) proteins also may provide detection of AD, specifically a 3-protein pattern consisting of low levels of Aβ and increased levels of total tau and hyperphosphorylated tau.[16] α-synuclein is related to Lewy body spectrum disorders. Secreted amyloid precursor protein alpha (sAPP-α) is related to the response of microglia to chronic inflammation and, while it may be found in AD, it has not been established as a significant biomarker.[17]

Sample Death Certificate/Cause of Death Statement:
Acute bronchopneumonia, due to:
Alzheimer disease

Manner of Death: Natural

Key Teaching Points:

- The most common immediate cause of death in patients with dementia is pneumonia.
- Alzheimer disease (AD) is the most common cause of dementia in the elderly.
- Pathologic hallmarks include:
  - Gross: Generalized (nonlobar) cerebral atrophy, most prominent in medial temporal areas
  - Microscopic: Senile plaques composed of extracellular deposits of Aβ (amyloid-beta) with or without dystrophic neurites (NPs and DPs, respectively), and neurofibrillary lesions including neuropil threads and intraneuronal neurofibrillary tangles; the major structural component of the dystrophic neurites of the plaque, neuropil threads and neurofibrillary tangles is tau
    - Silver stains and immunostains to Aβ and tau are needed to demonstrate lesions
- Deposition of Aß is the likely primary event in the pathogenesis of AD.
- AD is considered both a tauopathy and β-amyloidopathy since both tau and β-amyloid lesions characterize the pathologic lesions.
- Neurofibrillary pathology progresses in a predictable hierarchical order of involvement beginning in limbic areas (entorhinal cortex to hippocampus) and then advancing to association cortices and finally to primary sensory cortices.
  - This progression forms the basis of the Braak and Braak staging of the severity of AD and a component of the current NIA-Reagan criteria for the pathological diagnosis of AD.

- Biomarkers supporting the clinical diagnosis of AD include:
  - Hippocampal atrophy on MRI
  - Regional reduction of blood flow/metabolism on functional studies
  - Increased Pittsburg compound B (PIB) labeling on PET
  - CSF profile with low Aβ and increased tau levels

References:

1. Fu C, Chute DJ, Farag ES, et al. Comorbidity in dementia: an autopsy study. *Arch Pathol Lab Med*. 2004:128;32-38.
2. Mukhopadhyay S, Katzenstein AA. Pulmonary disease due to aspiration of food and other particulate matter: a clinicopathologic study of 59 cases diagnosed on biopsy or resection specimens. *Am J Surg Pathol*. 2007:31;752-759.
3. Morgenthau AS, Padilla ML. Spectrum of fibrosing diffuse parenchymal lung disease. *Mt Sinai J Med*. 2009:76;2-23.
4. Gordon IO, Sitterding S, Mackinnon C, et al. Update in neoplastic lung diseases and mesothelioma. *Arch Pathol Lab Med*. 2009:133;1106-1115.
5. Feng Z, Zhao G, Yu L. Neural stem cells and Alzheimer's disease: challenges and hope. *Am J Alzheimer Dis Other Demen*. 2009:24;52-57.
6. Duyckaerts C, Dickson DW. Neuropathology of Alzheimer's disease. In: Dickson DW, ed. *Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders*. Basel, Switzerland: ISN Neuropath Press; 2003:47-65.
7. Braak H, Braak E. Neuropathological staging of Alzheimer-related changes. *Acta Neuropathol.* 1991;82:239-259,
8. Consensus recommendations for the postmortem diagnosis of Alzheimer's disease. The National Institute on Aging, and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease. *Neurobiol Aging.* 1997;18(suppl 4):S1–2.
9. Roher AE, Esh CL, Kokjohn TA, et al. Amyloid beta peptides in human plasma and tissues and their significance for Alzheimer's disease. *Alzheimer's & Dementia*. 2009;5:18-29.
10. Dickson DW, Crystal HA, Mattiace LA, et al. Identification of normal and pathological aging in prospectively studied nondemented elderly humans. *Neurobiol Aging*. 1992;13:179-189.
11. McKeith IG, Dickson DW, Lowe J, et al. Diagnosis and management of dementia with Lewy bodies: third report of the DLB Consortium. *Neurol.* 2005;65:1863-1872.
12. Jellinger KA. Morphologic diagnosis of "vascular dementia"-a critical update. *J Neurol Sci*. 2008;270:
    1-12.
13. Brown P, Gibbs CJ Jr, Rodgers-Johnson P, et al. Human spongiform encephalopathy: the National Institutes of Health series of 300 cases of experimentally transmitted disease. *Ann Neurol.* 1994;35:513-529.
14. Jack CR Jr, Petersen RC, Xu YC, et al. Medial temporal atrophy on MRI in normal aging and very mild Alzheimer's disease. *Neurology*.1997;49(3):786-794.
15. Bastos-Leite AJ, van Waesberghe JH, Oen AL, et al. Hippocampal sulcus width and cavities: comparison between patients with Alzheimer disease and nondemented elderly subjects. *Am J Neuroradiol*. 2006;27:2141-2145.
16. Zhang J, Sokal I, Peskind ER, et al. CSF multianalyte profile distinguishes Alzheimer and Parkinson diseases. *Am J Clin Pathol*. 2008;129:526-529.

17. Barger S, Basile A. Activation of microglia by secreted amyloid precursor protein evokes release of glutamate by cystine exchange and attenuates synaptic function. *J Neurochem*. 2008;76:846-854.