

Amyotrophic Lateral Sclerosis: The Role of the Pathologist

By Matthew D. Cykowski, MD

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease resulting from the loss of upper motor neurons (UMN) and lower motor neurons (LMN). ALS is progressive, and patient survival is typically three to five years even with optimal therapeutic interventions. ALS is remarkable for its clinical, genetic, and pathologic heterogeneity. Patients may present with UMN and/or LMN findings in a single extremity, findings in both upper and lower extremities, or alternately, “bulbar symptoms” characterized by difficulty swallowing, speaking, or breathing. Other patients have significant cognitive impairment with approximately 15% meeting criteria for comorbid frontotemporal dementia (ALS/FTD). ALS is genetically heterogeneous with a *de novo* sporadic form (90% of patients) and familial forms (10%). The latter occur as rapidly progressive, autosomal dominant disorders with an earlier age of onset and involve the genes *SOD1*, *FUS*, *TARDBP*, and *C9orf72*, among others, with *C9orf72* alterations being most common.

The care of an ALS patient requires a team of physicians and therapists, typically under the guidance of a neurologist. This team often includes pathologists. ALS patients often require laboratory medicine involvement in their care after diagnosis in the evaluation of disease-related complications. Though uncommon, a skeletal muscle biopsy may be performed at the time of diagnosis as well. In these cases, pathologists assess the muscle for histologic features of neurogenic atrophy/denervation, while excluding other primary muscle diseases that may result in weakness, such as inflammatory, metabolic, or mitochondrial myopathies.

Pathologists also are involved in the autopsy confirmation of ALS. Characteristic findings include spinal cord atrophy, ventral spinal nerve root and cranial nerve root atrophy, and muscular atrophy. Macroscopically evident thinning of the precentral gyrus is uncommon but may be seen, reflecting a profound loss of UMNs within frontal cortex. Microscopically, there may be a loss of motor neurons in frontal cortex, cranial nerve motor nuclei (though cranial nerves III, IV, and VI are often spared), and lamina IX of the spinal cord ventral gray horn. Neuronal inclusions, including small intracytoplasmic inclusions termed Bunina bodies, reactive gliosis, and microglial activation may also be seen. Secondary degeneration of white matter tracts is common and prominent in the lateral and ventral funiculi of the spinal cord containing the lateral and anterior corticospinal tracts, respectively. Antibodies to TAR DNA-binding protein of 43 kDa (TDP-43) are routinely used to identify the ubiquitinated neuronal inclusions of ALS. These inclusions may be surprisingly extensive in noncanonical brain regions (eg, hippocampus, subcortical nuclei), reflecting the current understanding that ALS is a multisystem disorder in many patients. Other antibodies are available to

histologically confirm forms of ALS that are TDP-43-immunonegative (eg, familial ALS with *SOD1* mutation).

The pathologist holds another important role of working with neurologists and research teams to ensure proper storage and utilization of patient samples for future study. Clinical, genetic, and pathologic studies of ALS greatly benefit from well-curated tissue banks. This resource, which requires significant input from pathology, facilitates basic science and translational research efforts that will improve the diagnosis and treatment of this disease.

References

1. Al-Chalabi A, Jones A, Troakes C, King A, Al-Sarraj S, van den Berg LH. The genetics and neuropathology of amyotrophic lateral sclerosis. *Acta Neuropathol.* 2012;124(3):339–52. doi:10.1007/s00401-012-1022-4.
2. Brettschneider J, Del Tredici K, Toledo JB, et al. Stages of pTDP-43 pathology in amyotrophic lateral sclerosis. *Ann Neurol.* 2013;74(1):20–38. doi:10.1002/ana.23937.
3. Dickson D, Weller RO. *Neurodegeneration: The Molecular Pathology of Dementia and Movement Disorders*. 2nd ed. Chichester, West Sussex: Wiley-Blackwell: International Society of Neuropathology; 2011.
4. Phukan J, Pender NP, Hardiman O. Cognitive impairment in amyotrophic lateral sclerosis. *Lancet Neurol.* 2007;6(11):994–1003.
5. Ravits J, Appel S, Baloh RH, et al. Deciphering amyotrophic lateral sclerosis: what phenotype, neuropathology and genetics are telling us about pathogenesis. *Amyotroph Lateral Scler Frontotemporal Degener.* 2013;14 (Suppl 1):5–18. doi:10.3109/21678421.2013.778548.
6. Takei H, Bhattacharjee MB, Adesina AM. Pathology of motor neuron disorders. Medscape website. <http://emedicine.medscape.com/article/2111360-overview>. Updated April 29, 2014. Accessed August 18, 2014.