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63-YEAR-OLD WOMAN WITH DYSPHONIA, DYSPHAGIA, AND SLEEP APNEA

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CLINICAL HISTORY

An obese and hypertensive 63-year-old Caucasian woman presented with persistent and progressively worsening exertional dyspnea, occasionally accompanied by anginal chest pain as well as dysphonia, hoarseness, dysphagia, complaints of lower extremity weakness, and documented mild chronic L5-S1 denervation. Work-up revealed moderate obstructive ventilatory defect, borderline restrictive defect, and variable extrathoracic obstruction. Weakness and progressively poor quality of sleep characterized by sleep-disordered breathing, increased daytime somnolence, fatigue upon waking and increased snoring were added to her initial complaints. A sleep study established the diagnosis of severe obstructive sleep apnea. Treatment with continuous positive airway pressure (CPAP) produced significant improvement in her energy levels, more restful sleep and less fatigue, but her dyspnea worsened. A new cycle of cardiac and respiratory evaluation was positive for mild pulmonary hypertension and negative for myocardial ischemia and pulmonary fibrosis. Shortly after these last assessments, and two to three years after onset of symptoms, the patient died suddenly in her sleep.

NEUROPATHOLOGY

The general autopsy revealed emphysema and cardiomegaly with no coronary atherosclerosis and no acute pulmonary or cardiac disease to explain sudden death. Gross examination of the brain showed only a slightly flattened left inferior olive. The spinal cord appeared normal. Microscopic examination confirmed mild, patchy neuronal loss in the left olive. Neuronal loss was prominent in the anterior horns of the spinal cord, with relatively few remaining neurons (arrows, Figure 1a). There was no neuronal loss in substantia nigra, striatum, cerebellum, or basis pontis, with only modest reactive astrocytosis and rare neuronal ballooning in the pons, medulla and spinal cord. The corticospinal tracts were unremarkable.

Immunohistochemical staining for α-synuclein highlighted intracytoplasmic inclusions in the midbrain, pons, medulla, cerebellum and spinal cord. The inclusions were most numerous in the medulla (Figure 1b) and the gray matter of the spinal cord (Figure 1c). The inclusions also stained for ubiquitin but not tau. There were no ubiquitin-positive inclusions in motor neurons to suggest amyotrophic lateral sclerosis. The diaphragm showed scattered groups of atrophic skeletal muscle fibers (Figure 1d). What is your diagnosis?

Figure 1.
**DIAGNOSIS**

Multiple system atrophy.

**DISCUSSION**

Multiple system atrophy (MSA) is a progressive neurodegenerative disease characterized by glial cytoplasmic inclusions (GCIs) in oligodendroglia of the brain and spinal cord. GCIs consist of fibrillar aggregates of α-synuclein protein that are also immunoreactive for ubiquitin (8). Occasional immunoreactive inclusions may be found in astrocytes; neuronal cytoplasmic and nuclear inclusions are also occasionally seen (9).

Current consensus criteria recognize two forms of MSA: MSA with predominant parkinsonian symptoms (MSA-P) and MSA with predominant cerebellar ataxia (MSA-C) (4). Autonomic failure is most typical of MSA-P but can occur with either form. The clinical picture depends on the specific areas of brain and spinal cord affected in a given individual, and clinical and pathologic overlap between these forms is common. Bladder dysfunction is a common initial complaint. Most patients develop parkinsonism at some stage, with symptoms of bradykinesia with rigidity, tremor, and/or postural instability. Evidence of autonomic failure includes orthostatic hypotension and syncope. Cerebellar disease may manifest as gait ataxia, ataxia of speech, or oculomotor dysfunction. Lower motor neurons signs may be seen (9).

MSA is also causes extrathoracic respiratory compromise. Respiratory features include stridor, inspiratory sigh, and new or increased snoring. Symptoms manifest during sleep, such as obstructive sleep apnea and rapid eye movement (REM) sleep behavior disorder, are common (1, 2, 3, 5). The pathophysiologic abnormalities underlying sleep apnea and laryngeal stridor in patients with MSA can lead to sudden death (7). Central sleep apnea in MSA has been attributed to loss of ventral medullary neurons and degeneration of the pontomedullary network. The ventilatory response to hypoxia may also be affected and contribute to the apnea (1). Laryngeal stridor in MSA may originate from paradoxical tonic contraction of adductor laryngeal muscles with or without abnormal relaxation or paralysis of abductor muscles (1).

In summary, this patient presented with exertional dyspnea and developed dysphagia, dysphonia, variable extrathoracic respiratory obstruction, and severe obstructive sleep apnea. While her clinical examination did not document cerebellar or extrapyramidal abnormalities, her signs and symptoms have all been suggested as “red flags” for MSA (6), and the neuropathologic examination showed the characteristic GCIs of this disorder, particularly in the medulla and spinal cord. The medullary involvement explained her neurologic and respiratory signs. Her obstructive sleep apnea could also be explained on the basis of MSA and was the most likely cause of her sudden death. The relatively mild denervation of the diaphragm played no more than a minor role in her death, though her motor neuron loss was responsible for at least part of her weakness. Her case reflects an unusual presentation of a classic disease and illustrates the importance of a complete autopsy, including a complete neuropathologic examination, in cases of sudden unexpected death.

**REFERENCES**