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PARANEOPLASTIC CEREBELLAR ATAXIA WITH CENTRAL HYPOVENTILATION

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We describe a patient with small cell lung cancer with anti-Hu paraneoplastic cerebellar degeneration and central hypoventilation syndrome. This highlights the insidious clinical presentation of central hypoventilation and raises awareness of this condition as a paraneoplastic phenomenon. This case also highlights the complex circuitry of automatic respiration in the brainstem and the potential role of the cerebellum. We emphasize the difficulties in managing paraneoplastic central hypoventilation.

Case report. A 52-year-old woman presented to her oncologist with complaints of fatigue and poor memory. She was a smoker and had small cell carcinoma diagnosed 13 months ago on CT chest and confirmed histologically on fine needle biopsy. PET demonstrated it was confined to the right hilum and mediastinal lymph nodes with no distant disease. She was treated with chemotherapy (cisplatin and etoposide) and concurrent radiotherapy. She had prophylactic cranial irradiation 6 months after diagnosis with no acute or early delayed side effects.

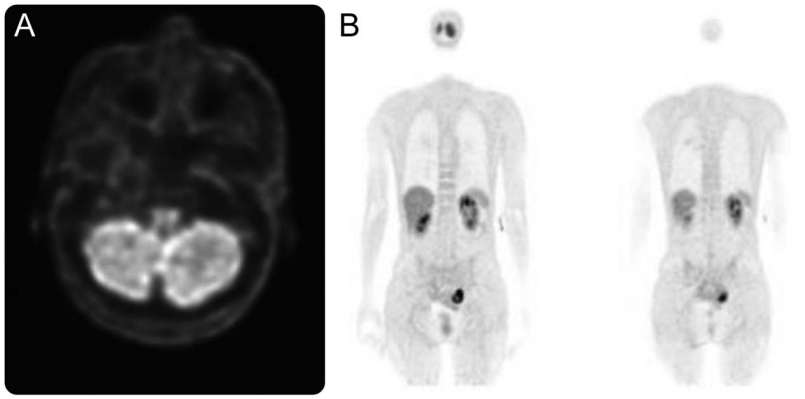
The patient presented 13 months after diagnosis with poor memory and feeling "vague." Over the next month, the patient developed dizziness and unsteady gait. Her clinical examination revealed a broad-based ataxic gait, upbeat nystagmus, and dysdiadochokinesis. There were no other cranial nerve abnormalities. MRI brain was unremarkable. CSF demonstrated 10 leukocytes (86% lymphocytes, 14% monocytes), 146 erythrocytes, protein 1.01 g/L, and glucose 4.1 mmol/L. Anti-Hu antibodies were detected in CSF and serum. PET scan demonstrated glucose hypermetabolism in the cerebellum and in the left ovary (figure). A diagnosis of paraneoplastic cerebellar syndrome was made. The patient was treated with methylprednisolone 1 g for 5 days. A left salpingo-oophorectomy was performed and histology confirmed metastatic small cell carcinoma. Postoperatively, she was hypoxic and hypercapneic, with a $PaCO_2$ of 70–80 mm Hg. She had apneic episodes when asleep and her ventilation improved when alert and when exercising. She was diagnosed with central hypoventilation and commenced on noninvasive ventilation. IV immunoglobulin was given for 5 days (0.4 mg/kg). Repeat serum anti-Hu antibodies were detected 1 month later. The patient was confused and agitated and unable to comply with bilevel positive airway pressure, and she was mechanically ventilated. The patient was unable to be extubated and a tracheostomy was performed. When the sedation was weaned, the patient became agitated and compromised the tracheostomy. After 4 weeks of mechanical ventilation and sedation, a decision was made with the family to de-cannulate the patient and the patient died. An autopsy was declined by the family.

Discussion. This is a case of anti-Hu paraneoplastic cerebellar syndrome and central hypoventilation. Central hypoventilation can be inherited or acquired. The inherited form is seen in congenital central hypoventilation with mutations in the paired-like homeobox *PHOX2B* gene. Acquired central hypoventilation has been associated with brainstem tumors and ischemic lesions and Chiari malformations. Central hypoventilation has been reported in anti-Hu paraneoplastic brainstem encephalomyelitis[1] and in patients later identified as having anti-NMDA encephalitis.[2] To our knowledge, there are no reports of central hypoventilation after prophylactic cranial irradiation and its effects on the brainstem and cerebellum are unknown.

The mechanism of central hypoventilation is thought to be disruption of the brainstem respiratory nuclei. The nuclei identified in respiration include the dorsal respiratory group in the nucleus of tractus solitarius, the pneumotaxic center or pontine respiratory group, and the ventral respiratory group.[3] The nuclei that are affected might correspond with the type of central ventilation disorder, either loss of automatic or voluntary breathing control, and could determine the therapeutic approach.[3] The pathologic involvement of these brainstem regions has been demonstrated in autopsy findings of a patient with anti-Hu-associated central hypoventilation:perivenous and parenchymal inflammatory infiltrates and severe neuronal loss in the medulla involving the 12th neuronal nuclei, inferior olives, nucleus ambiguus, and reticular system.[4]

The role of the cerebellum in control of respiration has been demonstrated in congenital central hypoventilation syndrome, in which the cerebellar cortex

Figure FDG-PET



(A) Bilateral cerebellar hypermetabolism. (B) Left posterior pelvis markedly glucose avid lesion.

and deep nuclei have decreased signaling in response to hypercapnea.[5] In mouse models of sudden infant death syndrome, mutant mice with Purkinje cell loss have shown impaired compensatory breathing responsiveness to hypercapnea.[6]

Chronic hypoventilation can present more insidiously than acute hypoventilation with morning headache, daytime fatigue, and mental status change. Patients with central hypoventilation have normal ventilation while awake but hypoventilate when asleep. The normal response to hypercapnia with increased ventilation is diminished. An arterial blood gas analysis and polysomnography can be used to identify this condition.

Treatment of the primary tumor does not always abolish the paraneoplastic syndrome. Immune therapies have minimal efficacy on paraneoplastic conditions with intracellular antigens. Central hypoventilation can be managed with noninvasive ventilation, but requires patient compliance. Congenital central hypoventilation has been managed with noninvasive ventilation, diaphragm pacing by phrenic nerve stimulation, tracheostomy, and home ventilation. There are reports of phrenic nerve pacing for central hypoventilation from brainstem encephalitis.[7]

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