Clinical Reasoning:

Stepwise paralysis in a patient with adenocarcinoma of lung

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SECTION 1

A 54-year-old man presented with pain in the left chest for 3 days. His medical history was remarkable for hyperlipidemia managed with diet and statin. He denied tobacco smoking and consumption of alcohol. Physical examination was unrevealing. The patient was diagnosed with an adenocarcinoma of the lung harboring an epidermal growth factor receptor (EGFR) mutation that metastasized to T2-T4 levels. He was treated with radiotherapy and dexamethasone followed by Gefitinib.

In the subsequent weeks, the patient developed flaccid paraparesis with Medical Research Council (MRC) graded strength of 3/5 in most muscles of the lower limbs and normal power (MRC of 5/5) in the upper limbs. Deep tendon reflexes were symmetrical and grade 1+ in the lower limbs and 2+ in the upper limbs. Plantar responses were flexor. Sensory examination revealed impaired pinprick caudal to the T4 level. Cranial nerve examination was unremarkable. The patient was diagnosed with a T2-T4 pathologic fracture causing spinal cord com-

pression. He underwent urgent T2-T4 laminectomy, T3-T4 vertebrectomy, and resection of epidural tumor with partial recovery (MRC of 4/5 at most in muscles of the lower limbs and MRC of 5/5 in the upper limbs) after rehabilitation.

Approximately 2 weeks after his surgery, the patient developed rapidly progressive, severe weakness affecting lower and upper limbs with increasing respiratory discomfort over a 3-day period. The patient was intubated and transferred to the intensive care unit due to respiratory distress. He was alert without obvious cranial nerve dysfunction. Neurologic examination was remarkable for a severe, flaccid tetraparesis (MRC of 1/5 at most in all tested muscles in the lower limbs and MRC of 2/5 at most in all tested muscles in the upper limbs) in addition to diffuse areflexia and neutral plantar responses.

Questions for consideration:

1. What is your differential?
2. What investigations would you recommend?

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SECTION 2

In cases of rapidly progressive tetraparesis, the clinician contemplates neurologic dysfunction at different levels of the nervous system from the motor and sensory long tracts to the spinal nerve roots, peripheral nerves, neuromuscular junction, and muscles. The nonpyramidal distribution of the weakness, lack of involvement of other supratentorial functions, and normal cranial nerve examination argued against a supraspinal localization. A reasonable etiologic differential diagnosis would include (1) progression of the spinal cancer with cervical involvement cranial to C5; (2) leptomeningeal metastasis; (3) Guillain-Barré syndrome (acute inflammatory demyelinating polyradiculoneuropathy [AIDP]) secondary to postinfectious state, paraneoplastic disease, or chemotherapy; (4) paraneoplastic neuromuscular junction disorders, e.g., Lambert-Eaton myasthenic syndrome; and (5) drug-induced myopathy due to steroids or statin. It is also worth mentioning metabolic causes of weakness with hyporeflexia or areflexia including

electrolyte disturbances (e.g., hyperpotassemia, hypermagnesemia).¹

The clinician should initially consider laboratory tests and neuroimaging of the spine followed by lumbar puncture with CSF analysis and electrodiagnostic studies. Indeed, the initial investigations revealed normal blood tests (i.e., complete blood count, electrolyte concentrations, creatine kinase, creatinine, and liver functions), and no evidence of progression of the metastatic spine disease on MRI (figure 1). CSF analysis was unrevealing for cell count and differential, biochemistry, infectious panel, and cytology. Of note, CSF was collected 9 weeks after cancer diagnosis and only 3 days following the first symptom the tetraparesis. Electrodiagnostic testing revealed (1) markedly reduced median, ulnar, and tibial compound motor unit potential (CMAP) amplitudes with prolonged distal latency and conduction velocity slowing; (2) conduction block of the ipsilateral ulnar nerve between the below elbow site and upper arm; (3) nonrecordable ipsilateral fibular motor responses at the extensor digitorum brevis and marked reduced CMAP and conduction block in the tibialis anterior at the knee; (4) absent ipsilateral median and ulnar F-wave responses; (5) absent ipsilateral median and sural sensory nerve action potentials; and (6) evidence of active denervation in the ipsilateral tibialis, soleus, and first dorsal interosseous muscles with relative preservation of the ipsilateral vastus medialis and pronator teres muscles (distal > proximal gradient of axonal loss) on needle examination.

Questions for consideration:

1. What is your interpretation?
2. What are your next steps in management?

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Figure 1 MRI of the cervical and high thoracic spine

Sagittal T1-weighted (A) and T2-weighted (B–D) MRI of the cervical and high thoracic spine show metastatic cancer infiltrating the vertebral bodies and compression of the spinal cord from T2 to T4 levels. There was no significant interval change when compared with the patient's initial MRI (not shown).

SECTION 3

Electrodiagnostic testing revealed a length-dependent, segmental, primarily demyelinating polyneuropathy, which was suggestive of AIDP. The patient denied history of recent symptoms and signs of infectious diseases. Paraneoplastic panel was negative for anti-Hu, anti-Yo, anti-Ri, anti-CASPR2, and anti-LGI1 antibodies. Gefitinib was held.

Given the diagnosis of AIDP, IV immunoglobulin therapy (1 g/kg for 2 days) was instituted. Over the following 4 weeks, the patient recovered

considerably from his motor deficits (MRC of 2/5 at most in the lower limbs and MRC of 4+/5 in most of the upper limbs) with partial recovery of the deep tendon reflexes of the upper limbs. He was eventually transferred to a rehabilitation center.

Questions for consideration:

1. What other neurologic complications should you expect?
2. How would you manage these?

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SECTION 4

In addition to the sensorimotor deficits, patients with high thoracic or cervical lesions (at T6 or more cranial level) can develop cardiovascular complications due to loss of supraspinal sympathetic control. Furthermore, this patient was diagnosed with AIDP, which also affects motor, sensory, and autonomic nervous systems.

The patient initially presented with labile arterial blood pressure with a trend to hypotension and frequent hypertensive episodes (figure 2A). The patient showed no clinical or laboratory findings

suggestive of shock. While low resting arterial blood pressure can be seen in patients with high thoracic spinal cord compression or AIDP, the sudden-onset hypertensive episodes are characteristic of autonomic dysreflexia that commonly occurs in patients with severe cervical or high thoracic spinal cord injury (SCI). The patient underwent a search for potential triggers of autonomic dysreflexia caudal to the level of SCI. Abdominal CT revealed fecal impaction (figure 2B). The resolution of the impaction was accompanied by stabilization in blood pressure (figure 2C).

Figure 2 Variations in blood pressure (BP) and heart rate

Hourly variations in BP and heart rate within 24 hours before (A) and after (C) treatment of fecal impaction; autonomic dysreflexia characterized by hypertensive episodes is seen (A). The axial and coronal CT images of the abdomen show impaction in the descending colon and rectum (B).

DISCUSSION This case illustrates potential neurologic complications of lung cancer: metastatic spinal cord compression (MSCC) and AIDP. Both conditions are associated with motor, sensory, and autonomic dysfunction.

The occurrence of MSCC was estimated to be between 0.23% and 0.36% of patients with cancer.^{2,3} Lung, prostate, and breast cancer account for approximately two-thirds of cases.² Nonoperative treatment of MSCC with corticosteroids and radiotherapy was considered the standard of care until the 1990s. The benefits of direct decompressive surgical resection followed by radiotherapy for management of patients with a single area of MSCC were shown in a randomized clinical trial in 2005.⁴ These benefits included a longer survival time, more commonly remaining ambulatory and continent, and improved pain symptoms when compared with patients who underwent radiotherapy alone.⁴ Although the adoption of this combined palliative approach would most likely increase health care costs, its benefits should be compassionately considered before making treatment decisions.⁵ While several specialists treating these patients widely recommend the combined palliative approach, there is no consensus on its indication for a multilevel MSCC. The most recent Cochrane Review indicated that “decompressive surgery followed by radiotherapy may benefit ambulant and non-ambulant adults younger than 65 years of age, with poor prognostic factors for radiotherapy, a single area of compression, paraplegia for less than 48 hours, and a predicted survival of more than 6 months.” Given that this patient had multilevel metastatic spine cancer with no neurologic deficits at presentation, a multidisciplinary team recommended radiotherapy and corticosteroid therapy followed by chemotherapy.

The potential clinical consequences of loss of supraspinal sympathetic control are well-recognized among patients after traumatic, severe, cervical, or high thoracic SCI.^{6,7} In addition to low resting blood pressure and orthostatic hypotension, individuals commonly develop hypertensive episodes associated with a variety of autonomic symptoms and signs (i.e., autonomic dysreflexia).^{6,7} The management of an episode of autonomic dysreflexia includes cardiovascular monitoring, assumption of the sitting position, loosening clothing or constrictive devices, and searching for potential triggers such as pressure sores, urinary complications, and other abdominal pathologies.⁶ Pharmacologic treatment is recommended only if the patient has persistently elevated systolic pressure (≥ 150 mm Hg). Despite the severe potential complications of autonomic dysreflexia (e.g., retinal detachment, posterior reversible encephalopathy syndrome, seizures, stroke, and death), studies have shown that this entity is often unrecognized by

individuals with SCI, caregivers, and health care professionals.⁶

AIDP is also recognized as a cause of motor and sensory dysfunction as well as autonomic instability. The patient showed significant neurologic recovery after IV immunoglobulin therapy. Neurologists should have a high index of suspicion for paraneoplastic syndromes when evaluating a patient with known or suspected malignancy, even though only up to 1% of patients with cancer have an obvious paraneoplastic disorder.⁸ Moreover, meningeal disease, coagulopathy, metastasis, toxic, metabolic, and chemotherapy-induced causes should be ruled out before attributing a paraneoplastic diagnosis.^{8,9} While positive antibodies in patients with a suspected paraneoplastic syndrome are generally diagnostic, undetected antibodies occur in approximately 20% of patients with paraneoplastic syndromes of the CNS and most of the patients with paraneoplastic syndromes of the peripheral nervous system.^{8–10} CSF analysis is advisable in cases of a suspected paraneoplastic syndrome involving the CNS, nerve roots, or spinal sensory ganglia. In 90% of those cases, there is an inflammatory CSF change including lymphocytic pleocytosis, oligoclonal bands, and/or elevated protein, even though the sensitivity decreases with time. Normal CSF analysis is seen in only 7% of cases.⁸

The association of non-small-cell or small-cell lung carcinoma with AIDP has been reported in few cases.^{9,11–14} While coincidental occurrence of postinfectious AIDP and lung cancer is possible, the search for a paraneoplastic cause or drug side effect seems more appealing because “plurality must not be posited without necessity” (Occam’s razor).¹⁵ In a recent publication, a patient with adenocarcinoma of lung developed AIDP that was attributed to CASPR2 antibodies.¹³ Our patient tested negative for voltage-gated potassium channel antibodies (i.e., anti-CASPR2 and anti-LGI1) and anti-Hu antibodies, which are more commonly seen in patients with paraneoplastic peripheral neuropathy due to lung cancer.¹⁶ Another potential but rare cause of AIDP important in our case is the presumed association of Gefitinib with AIDP. A single case of AIDP has been noted as a potential side effect of the drug. Of note, Gefitinib is a tyrosine kinase inhibitor that has been recently approved by the Food and Drug Administration as a first-line option for the treatment of patients with advanced non-small-cell lung cancer with mutated EGFR, due to the improvement of progression-free survival.¹⁷

This case emphasizes a need for a greater awareness of potential secondary complications of patients with spinal metastatic lung cancer. Occam’s razor should always be used, but there is not always a clean shave. Similar to neurologic presentations of

HIV, parsimony of localization and diagnosis is not always prudent. Early recognition and treatment of AIDP associated with cancer can prevent serious consequences of a potentially reversible disease. Timely diagnosis of episodes of autonomic dysreflexia can prevent complications of this life-threatening entity.

AUTHOR CONTRIBUTIONS

Dr. Furlan was responsible for design and conceptualization of the study, analysis and interpretation of the data, draft and revisions of the manuscript. Dr. Robinson was responsible for design and conceptualization of the study, analysis and interpretation of the data, draft and revisions of the manuscript. Dr. Murray was responsible for design and conceptualization of the study, analysis and interpretation of the data, draft and revisions of the manuscript.

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