Metastatic esophageal cancer presenting as shock by injury of vagus nerve mimicking baroreceptor reflex

A case report

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Abstract
Rationale: Neurogenic shock is generally typified by spinal injury due to bone metastases in cancer patients, but continuous disturbance of the vagus nerve controlling the aortic arch baroreceptor can cause shock by a reflex response through the medulla oblongata.

Patient concerns: A 43-year-old woman with dysphagia presented to our hospital. Computed tomography showed a primary tumor adjacent to and surrounding half the circumference of the descending aorta, and multiple cervical lymph node metastases, including a 55 × 35-mm lymph node overlapping the root of the left vagus nerve. Squamous esophageal cancer (T4bN3M1, stage IV) was diagnosed. Whereas shock status initially appeared soon after left cervical pain, suggesting pain-induced neurally-mediated syncope, sustained bradycardia and hypotension occurred even after alleviation of pain by opioids.

Diagnosis: Disturbance of the left vagus nerve associated with the aortic arch baroreceptor by a large left cervical lymph node metastasis was considered as the cause of shock, pathologically mimicking the baroreceptor reflex.

Interventions: Systemic steroid administration was performed, and radiotherapy for both the primary site and lymph node metastasis was started 2 days after initiating steroid treatment.

Outcomes: Four days after initiating steroid administration, hypotension and bradycardia were improved and stable.

Lessons: Disturbance of the vagus nerve controlling the aortic arch baroreceptor should be kept in mind as a potential cause of neurogenic shock in cancer patients, through a pathological reflex mimicking the baroreceptor reflex.

Abbreviations: ATP = adenosine triphosphate, CF = cisplatin and 5-fluorouracil, CT = computed tomography, DCF = docetaxel, cisplatin, and 5-fluorouracil, PS = performance status.

Keywords: baroreceptor reflex, esophageal cancer, lymph node, metastasis, shock, vagus nerve

1. Introduction

Baroreceptors exist at the aortic arch and carotid artery sinus, controlled by the vagus and glossopharyngeal nerves, respectively. Afferent impulses from baroreceptors in response to elevations of blood pressure are conveyed through these nerves to the medulla oblongata, leading to suppression of the sympathetic nervous system and activation of the parasympathetic nervous system, resulting in hypotension and bradycardia, respectively.

Syncope has various causes, including a pathological baroreceptor reflex, typically exemplified by carotid sinus syndrome.[1] Disturbance of the vagus and glossopharyngeal nerves that supply the baroreceptors can evoke syncope through excessive afferent impulses to the medulla oblongata. Previous reports have shown that cancers at the left hilum or left lobe of the lung can cause syncope by injuring aortic arch baroreceptors or the controlling vagus nerve.[2–4] Lung cancer-related syncope also appears associated with large tumors over about 40 mm in diameter,[2] which seems to be sufficient size to injure the baroreceptors or controlling the vagus nerve.

Given that the esophagus is anatomically close to the trachea, heart, and descending aorta, esophageal cancer can sometimes perforate or cause bleeding from these organs. On the contrary, the esophagus is anatomically distant from the aortic arch. Accordingly, direct invasion to the aortic arch baroreceptor and the controlling vagus nerve by a primary esophageal cancer is rare. Large lymph node metastases located near these structures,
however, can cause syncope through a reflex response in the medulla oblongata.

In this report, we present a case of neurogenic shock caused by a pathological baroreceptor reflex through disturbance of the vagus nerve supplying the aortic arch baroreceptors due to a large left cervical lymph node metastasis of esophageal cancer.

2. Case presentation

A 43-year-old woman presented to a local clinic with dysphagia in December 2015. She was referred to our hospital the following month. Gastrointestinal endoscopy revealed a mass occupying 80% of the lumen of the esophagus (Fig. 1A). Histological examination of a biopsy sample showed moderately differentiated squamous cell carcinoma. Upper gastrointestinal series also revealed an irregular mass at the middle thoracic esophagus (Figure 1B). Computed tomography (CT) showed a primary esophageal cancer adjacent to and surrounding half of the circumference of the descending aorta (Fig. 2A), multiple left cervical lymph node metastases, including a 55 × 35-mm lymph node metastasis overlapping the root of the left vagus nerve (Fig. 2B), and para-aortic lymph node metastasis, resulting in the diagnosis of stage IV middle thoracic esophageal cancer (cT4bN3M1 according to the TNM Classification of Malignant Tumors, 7th edition).

On day 4 after admission, soon after reporting strong pain on the left from neck to shoulder, she lost consciousness. At this time, the patient was hypotensive (68/34 mm Hg) and showed sinus bradycardia (heart rate 40 beats/min). About half an hour after administration of saline, she regained consciousness with
normal blood pressure (133/79 mm Hg) and heart rate (77 beats/ min). Loss of consciousness was initially attributed to neutrally-mediated syncope due to pain, although the period of unconsciousness lasted longer than the typical duration of syncope. The same day, she again lost consciousness soon after the complaint of acute pain. Pain had resolved by the time she regained consciousness, but hypotension and bradycardia continued, despite the disappearance of pain, suggesting a cause other than pain-induced neurally mediated syncope. Given that loss of consciousness and acute pain appeared with exacerbation of hypotension and bradycardia, continuous injection of dopamine was initiated to prevent further loss of consciousness. Administration of nonsteroidal anti-inflammatory drugs and application of a fentanyl transdermal patch with rescue usage of sublingual fentanyl was also started to prevent pain. However, the patient again lost consciousness and the fentanyl transdermal patch was therefore replaced by continuous infusion of morphine. Although no pain attacks recurred, sudden loss of consciousness with hypotension and bradycardia was observed. Changing the vasopressor from dopamine to continuous administration of norepinephrine improved hypotension and prevented loss of consciousness, but bradycardia continued. Episodes of loss of consciousness were then attributed to neurological shock via a pathological reflex response induced by the large left cervical lymph node metastasis disturbing the left vagus nerve supplying the aortic arch baroreceptors. Accordingly, we started systemic steroid treatment and radiotherapy for the primary esophageal cancer and lymph node metastasis after 2 days from initiation of steroid treatment. Four days after initiating steroid administration, hypotension and bradycardia were improved and stable, leading to discontinuation of norepinephrine. As pain appeared well-controlled, and performance status (PS) had improved to PS1, combined chemotherapy with cisplatin and 5-fluorouracil (CF; cisplatin at 70 mg/m² on day 1, 5-fluorouracil at 700 mg/m² on days 1–4 every 4 weeks) was added to radiotherapy 18 days after initiating radiotherapy. Although shock status did not recur after starting chemo-radiotherapy, the size of metastatic lymph nodes remained largely unchanged. Accordingly, we changed the chemotherapeutic regimen from CF to docetaxel, cisplatin, and 5-fluorouracil (DCF; docetaxel at 30 mg/m² on days 1 and 15, cisplatin at 80 mg/m² on day 1, 5-fluorouracil at 800 mg/m² on days 1–5, every 4 weeks). After 3 cycles of DCF, disease progression was observed and weekly paclitaxel (paclitaxel at 80 mg/m² on days 1, 8, 15, 22, 29, and 35, every 7 weeks) was started. However, about 1 month after initiating this regimen, disease progression was identified and she was discharged to palliative care at another clinic. Informed consent was obtained from the patient for the publication of the case details.

3. Discussion

Suppression of the sympathetic nervous system and activation of the parasympathetic nervous system through reflex responses to blood pressure elevation such as the baroreceptor reflex causes hypotension and bradycardia. In our case, a large left cervical lymph node metastasis over 35 mm in diameter extended from the left common cervical artery to the apex of the left lung. This area overlapped with the root of the left vagus nerve, a component of which supplies the aortic arch baroreceptor. Disturbance of the left vagus nerve was thus considered to have caused a reflex response through the medulla oblongata, mimicking the baroreceptor reflex response to an afferent impulse.

Previous reports have shown that lung cancer around the hilum or upper lobe of the left lung can cause bradycardia and hypotension through disturbance of the aortic arch baroreceptors and corresponding vagus nerve. Furthermore, carotid sinus syndrome represents a similar phenomenon involving compression of the baroreceptors of the carotid artery sinus, supplied by the glossopharyngeal nerve. This report offers a description of neurogenic shock caused by compression of the vagus nerve supplying aortic arch baroreceptors. The cases of lung cancer showing similar effects mentioned previously suggest that large tumors over 40 to 80 mm in diameter are a common, and these lesions are considered big enough to disturb baroreceptors or the associated vagus nerve. The lesion in our case was also 55 mm in diameter, bigger than the reported mean size of lymph node metastases from esophageal cancer (12.6 mm; range 3–30 mm). Although the prerequisites of both a large metastasis and a location overlapping the path of the vagus nerve root is rare in esophageal cancer, the possibility of neurogenic shock due to a pathological reflex needs to be considered in cases of patients with lymph node metastasis. On the contrary, the possibility of bradycardia and hypotension due to direct cardiac effects through injury to the efferent vagus nerve was considered low, because the sinoatrial node is predominantly supplied by the right vagus nerve. The patient initially presented with left neck pain just before shock status. Pain is generally the cause of neurally mediated syncope. The underlying physiology is not fully known, but pain is thought to induce a sympathetic surge resulting in vigorous cardiac contraction, finally leading to a vagus reflex activating the parasympathetic nervous system and suppressing the sympathetic nervous system. In our case, pain might have contributed to the shock status and also decreased the threshold for shock.

Two mechanisms underlying vagus nerve injury were considered: physical injury and injury resulting from the release of chemical mediators by tumor cells. Physical injury would directly affect the axons of the vagus nerve to evoke afferent impulses to the medulla oblongata. Furthermore, perineural invasion by tumor cells along the vagus nerve might impinge on the nerve.

Chemical injury, on the contrary, would involve mediators such as protons, adenosine triphosphate (ATP), endothelin, proteases, nerve growth factors, and neurotoxins, all of which are produced by tumors and have been studied as potential causes of cancer-related pain. As TRPV1, a receptor for protons, and P2X, a receptor for ATP, are expressed on axons, excitatory impulses evoked by stimulation of these receptors might be a cause of pathological reflexes. In such cases, targeting therapy for TRPV1 and P2X might offer effective treatment.

The treatment for neurogenic shock currently involves achieving euvolemia by hydration, followed by administration of vasopressors and inotropes. Dopamine was initially employed in the present case, but stable improvement of blood pressure proved difficult. The change to norepinephrine was effective, probably due to stronger vasopressor effects. Pacemaker implantation has been reported as ineffective, particularly in cases where vasodilation is the dominant pathology, because pacemakers improve bradycardia, but may not achieve sufficient vasoconstriction. As the primary cause of neurogenic shock, the approach for improving vagus nerve disturbance by lymph node metastasis is important. We performed radiotherapy followed by chemoradiotherapy, as modalities that are often effective against esophageal cancer. We also administered systemic steroids. Given neurogenic shock improved early, after only 2 sessions of radiotherapy, the steroid was thought to have
been effective for early improvement, while radiotherapy played a role in achieving continuous improvement. Whereas the mechanism underlying the efficacy of steroid treatment was considered to be improvement of edema around injured tissues and neuroprotective effects as seen in the treatment of superior vena cava syndrome and spinal compression, although the precise mechanisms remain unclear.[18–20]

4. Conclusions
We encountered a case of neurogenic shock attributed to lymph node metastasis of esophageal cancer disturbing the left vagus nerve. The present case is rare, but vagus nerve disturbance should be kept in mind as a potential cause of neurogenic shock through a pathological reflex mimicking the baroreceptor reflex.

References
[1] Chen-Scarabelli C, Scarabelli TM. Neurocardiogenic syncope. BMJ 2004;329:336–41.
[2] Jiang X, Zhao J, Bai C, et al. Small-cell lung cancer with recurrent syncope as the initial symptom: a case report and literature review. Mol Clin Oncol 2016;5:345–9.
[3] Koga T, Kasada S, Miyazaki N, et al. Angiology. Neurolymph node metastasis of esophageal cancer disturbing the left vagus nerve: a case report and review. Intern Med 2011;50:2367–9.
[4] Koukis P, Weidley SM, Yao Q, et al. Arterial baroreceptors in the management of systemic hypertension. Med Sci Monit 2010;16:RA1–8.
[5] Muppidi S, Gupta PK, Vernino S. Reversible right vagal neuropathy. Neurology 2011;77:1577–9.
[6] Dhar DK, Tachibana M, Kinukawa N, et al. The prognostic significance of lymph node size in patients with squamous esophageal cancer. Ann Surg Oncol 2002;9:1010–6.
[7] Casini A, Tschanz E, Dietrich PY, et al. Recurrent syncope due to esophageal squamous cell carcinoma. Case Rep Oncol 2011;4:433–8.
[8] George MS, Sackeim HA, Rush AJ, et al. Vagus nerve stimulation: a new tool for brain research and therapy. Biol Psychiatry 2000;47:287–95.
[9] Li S, Sun Y, Gao D. Role of the nervous system in cancer metastasis. Oncol Lett 2013;5:1001–11.
[10] Schmidt BL. The neurobiology of cancer pain. Neuroscientist 2014; 20:546–62.
[11] Schmidt BL, Hamamoto DT, Simone DA, et al. Mechanism of cancer pain. Mol Interv 2010;10:164–78.
[12] Patapoutian A, Tate S, Woolf CJ. Transient receptor potential channels: targeting pain at the source. Nat Rev Drug Discov 2009;8:55–68.
[13] Irnich D, Burgstahler R, Bostock H, et al. ATP affects both axons and Schwann cells of unmyelinated C fibres. Pain 2001;92:543–50.
[14] Lewis MA, Hendrickson AW, Moynihan TJ. Oncologic emergencies: pathophysiology, presentation, diagnosis, and treatment. CA Cancer J Clin 2011;61:287–314.
[15] Almquist A, Gornick C, Benson W Jr, et al. Carotid sinus hypersensitivity: evaluation of the vasodepressor component. Circulation 1985;71:927–36.
[16] Doctor of Medicine (2017) 96:49 Medicine
[17] Sasaki Y, Kato K. Chemoradiotherapy for esophageal squamous cell cancer. Jpn J Clin Oncol 2016;46:805–10.
[18] Rowell NP, Gleson FV. Steroids, radiotherapy, chemotherapy and stents for superior vena cava obstruction in carcinoma of the bronchus: a systematic review. Clin Oncol (R Coll Radiol) 2002;14:338–51.
[19] Ettinger AB, Portenoy RK. The use of corticosteroids in the treatment of symptoms associated with cancer. J Pain Symptom Manage 1988;3:99–103.
[20] McCurdy MT, Shanholz CB. Oncologic emergencies. Crit Care Med 2012;40:2212–22.