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Small-cell lung cancer with recurrent syncope as the initial symptom: A case report and literature review

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Abstract. Small-cell lung cancer (SCLC) presenting with syncope as the initial symptom is rare in adults. This onset of tumour-induced syncope cannot be screened or differentiated by coronary angiography, magnetic resonance angiography of the neck or 24-hour dynamic electrocardiogram. We herein describe the case of a 61-year-old man who presented with recurrent syncope that resolved after the first course of chemotherapy (carboplatin plus etoposide) for SCLC. A mass measuring 57x53 mm was identified in the left hilum, and a diagnosis of limited-disease SCLC (T4N2M0, IIIB) was made. Considering the rapid and complete remission after the treatment of the primary lesion, we hypothesised that the syncope was neurogenic and associated with cancer. Thus, 8 similar cases retrieved from PubMed were reviewed and, for the first time, the mechanism underlying the syncope was identified, which may involve tumour location, neurobiology and other inducing factors. Thus, for the treatment of such SCLC patients, standard chemotherapy is crucial for preventing syncopal attacks.

Introduction

Syncope is a common event, accounting for ~1% of all emergency visits to the hospital (1). There are three major categories of syncope, namely cardiac, orthostatic and neutrally mediated. Structural heart disease and orthostatic hypotension in elderly patients are associated with an increased mortality risk due to comorbidities (2). Syncopal attacks should draw clinicians' attention, as they may be associated with life-threatening events in such patients. Syncope is commonly attributed to cardiogenic or cerebral factors when considering differential diagnosis. It has been reported that episodic syncope is rarely caused by small-cell lung cancer (SCLC) (3), and clinicians should bear this possibility in mind, as it may be associated with life-threatening events. However, the mechanism underlying the occurrence of this type of syncope has not been fully elucidated. Therefore, we herein report a case treated at the Changhai Hospital of the Second Military Medical University (Shanghai, China) and review 8 cases (3-10) of SCLC accompanied with episodic syncope, with the aim of analysing potential mechanisms associated with lung tumour anatomy, the neurobiology of SCLC and the inducing factors of syncope, in order to provide optimal management recommendations for clinicians to identify and treat episodic syncope patients.

Case report

A 61-year-old man presented to the outpatient department with two incidents of recurrent loss of consciousness. The patient was admitted to our hospital for further evaluation of the syncopal attacks. Five months prior to admission, the patient had suffered a syncope after physical exertion; he reported dizziness and dyspnea, which lasted for 1 h, before he recovered consciousness spontaneously. One week prior to admission, the patient suffered a second syncope attack, with similar symptoms.

On physical examination, the patient appeared healthy; his pulse rate was 62 beats per minute, his blood pressure (BP) was 110/70 mmHg, his respiratory rate was 18 breaths per minute and his temperature was 36.2˚C. His body mass index was 21.8 kg/m^2, and the physical examination revealed no significant abnormalities. The sinus rhythm was found by 24-h dynamic electrocardiogram (ECG) to be 72 beats per minute, with 16 atrial premature beats, short paroxysmal atrial tachycardia, and 8 multifocal ventricular premature beats. An ultrasonic cardiogram (UCG) revealed mild mitral and tricuspid regurgitation with normal heart chamber size and wall movement. Coronary angiography was performed, as for syncope patients with myocardial ischaemia, with no obvious abnormalities detected.

The laboratory tests revealed elevated serum tumour marker levels [progastrinreleasing peptide, 398.47 pg/ml (normal range, 0-70 pg/ml); carbohydrate antigen 199, 3.46 U/ml (normal range, 0-37 U/ml); carcinoembryonic antigen, 1.39 ng/ml (normal range, 0-5 ng/ml); cytokeratin-19 fragment, 4.18 ng/ml (normal

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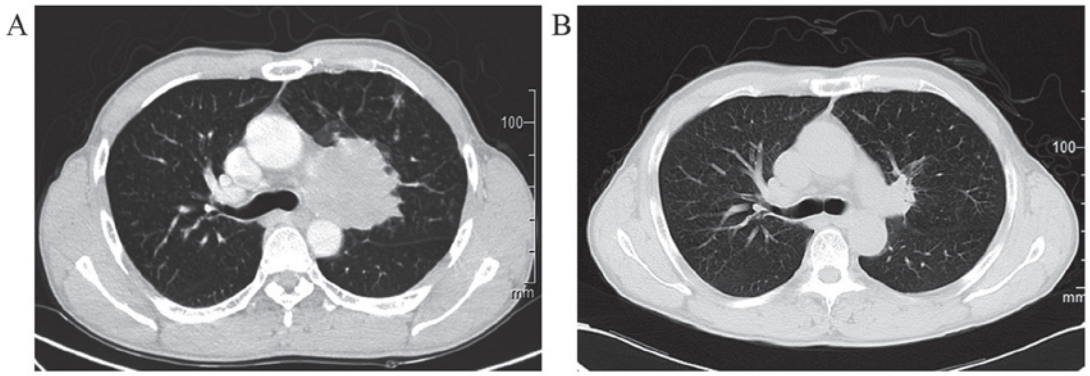

Figure 1. (A) Computed tomography (CT) image of the chest (axial view) showing a soft tissue mass measuring 7.2x2.4 cm in the left hilum; (B) Follow-up CT scan after 4 cycles of chemotherapy showing partial regression (PR), with the mass measuring 2.0x2.0 cm.

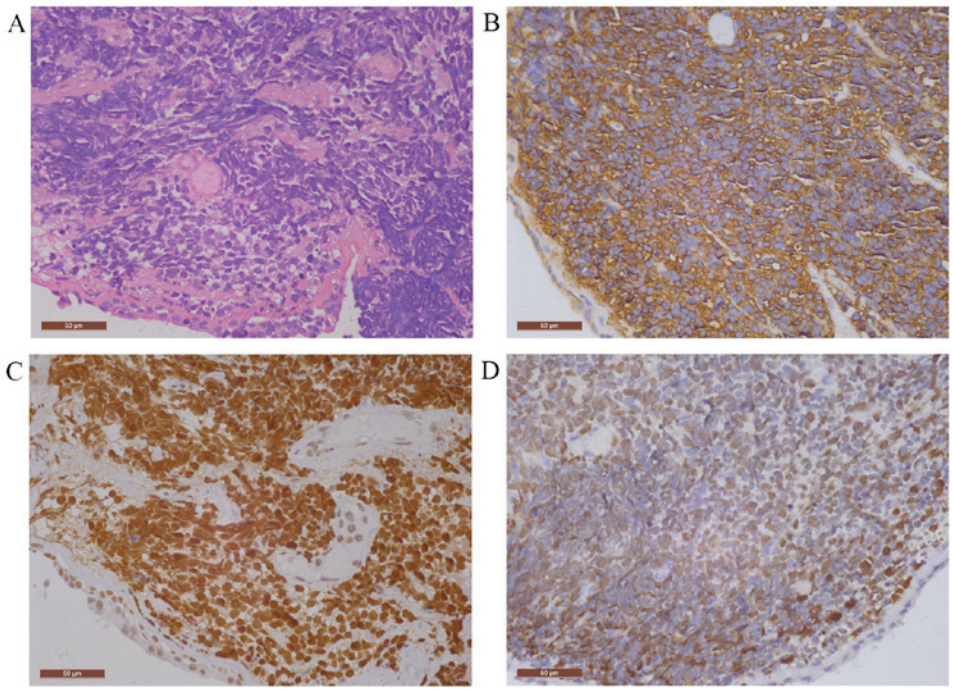

Figure 2. (A) Biopsy from the upper division bronchus of the left upper lobe using hematoxylin and eosin staining showing small tumour cells with scant cytoplasm; immunohistochemical analysis showing positive staining for (B) neuronspecific enolase, (C) thyroid transcription factor-1 and (D) Ki67.

range, 0-2.08 ng/ml); and neuron-specific enolase (NSE), 64.2 μg/l (normal range, 0-12.5 μg/l)]. Based on these tumour markers, a contrast-enhanced chest CT scan was scheduled and revealed a mass measuring 6.8x6.0 cm in the left hilum, accompanied by multiple enlarged mediastinal lymph nodes and multiple pulmonary bullae of the upper lobes bilaterally (Fig. 1A). Bronchoscopy revealed an upper left lobe neoplasm with surrounding infiltrative changes. Pathological diagnosis combined with immunohistochemistry for SCLC (Fig. 2) showed no evidence of metastasis. Therefore, the diagnosis was limited-disease SCLC (T4N2M0, IIIB).

On day 5 of admission, the patient stood up and, after taking a few steps, he experienced a third episode of syncope, with sweating and numbness of the extremities. The duration of the episode was ~1 min, and the BP dropped to 69/39 mmHg. An ECG showed sinus bradycardia at a rate of 48 beats per minute (Fig. 3). The BP and heart rate immediately increased following administration of a 0.5-mg intravenous bolus of atropine and continuous intravenous infusion of Ringer's lactate. A quick assessment of arterial blood gas, renal function and serum electrolytes did not reveal significant abnormalities. On the following day, a magnetic resonance angiography of the head and neck and a coronary angiography were performed, but no significant abnormalities were detected. According to the abovementioned tests, the possibility of a brain or cardiac origin of the syncope was excluded. Neurogenic syncope was suspected, associated with the SCLC. The patient was then administered chemotherapy (carboplatin injection 400 mg on day 1 and etoposide injection 100 mg on days 1-5). The patient exhibited a partial response (PR) according to the Response Evaluation Criteria in Solid Tumours (RECIST) guidelines, version 1.1 (11), with the mass measuring 2.0x2.0 cm (Fig. 1B) after 4 cycles of chemotherapy (carboplatin injection 400 mg on day 1 and etoposide injection 100 mg on days 1-5). The

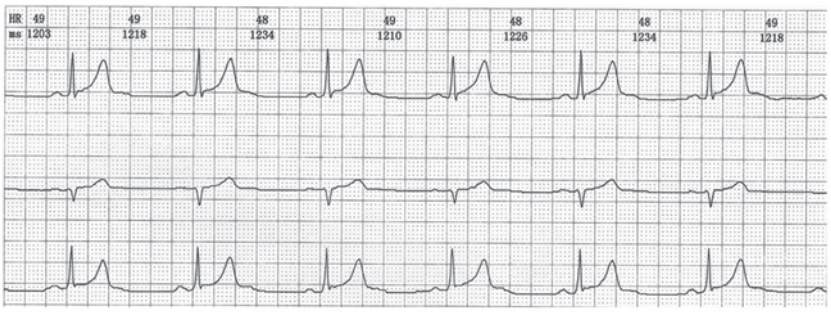

Figure 3. Electrocardiogram showing sinus bradycardia at a rate of 48 beats per min during the syncope attack.

patient refused further radiotherapy. After the first course of chemotherapy, no further syncopal attacks were observed. The patient received 6 courses of chemotherapy in our hospital and he was then discharged. Follow-up has been performed every 3 months by telephonical communication, and the disease is currently stable, with occasional cough and expectoration, for which he receives symptomatic treatment at a local hospital.

Written informed consent was obtained from the patient regarding the publication of the case details and accompanying images.

Discussion

Episodic syncope associated with SCLC is rare, and the association of episodic syncope with SCLC is not well understood. The definition of syncope is brief loss of consciousness with rapid spontaneous recovery, often triggered by transient reduction in cerebral perfusion (12). Based on the mechanisms involved, syncope may be divided into three major categories, namely cardiac, orthostatic and neutrally mediated syncope. Based on the various triggers, neutrally mediated syncope may be categorized into carotid sinus, vasovagal and situational syncope. In the present case, there was no evidence associating the episodic syncope with cardiac or cerebral mechanisms based on the MRA, UCG and CTA findings. Moreover, syncope was controlled after the first course of chemotherapy as the tumour size decreased. Therefore, we consider that this may have been a type of vasovagal syncope (VVS) associated with lung cancer.

Using PubMed, a literature search was performed, and only 8 previously reported cases of SCLC with recurrent syncope were identified (Table I) (3-10). A total of 9 cases are included in the review, including the present case, comprising a total of 8 men and 1 woman, with a mean age of 62.33±2.12 years.

According to Table I, almost all cases had a tumour located in the left hilum. This conclusion is similar to the findings reported by Shimizu *et al* (10). Yu *et al* and Wang *et al* (13,14) found that the cardiac branches arising from the left vagus nerve are lower and more closely located to the hilum compared with those from the right (Fig. 4). The cardiac branch of the left vagus nerve originates from the middle and lower part of the vagus nerve, whereas on the right side the cardiac branch mainly originates from the right recurrent laryngeal nerve, with the point of origin located higher. This is in agreement with the 88.9% incidence of the lesion in the left lung mentioned above, and indicates that the left cardiac branches are more easily infiltrated by lung cancer masses, which may account

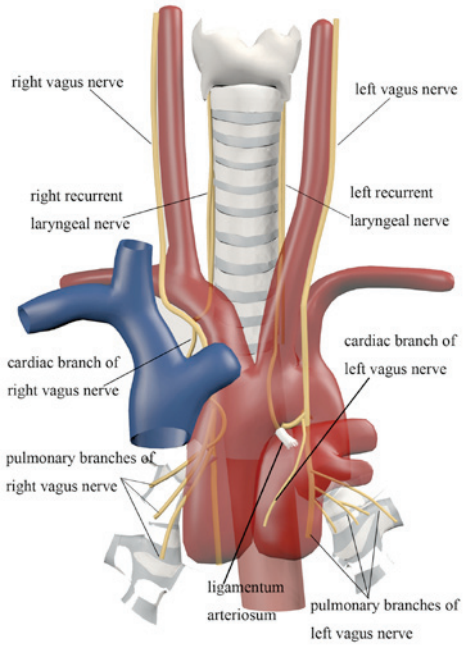

Figure 4. Anatomy of the vagus and recurrent laryngeal nerves, with their cardiac and pulmonary branches.

for the sinus bradycardia (48 beats/min) in our patient after the syncopal attack. Therefore, it is considered that the tumour location contributes to syncope. However, direct compression usually causes sustainable sinus bradycardia rather than episodic bradycardia.

Except for anatomical factors, SCLC, particularly of the oat cell type with neuroendocrine granules, may secrete and release hormones or peptides and other substances (such as catecholamines and 5-HT) (15), which play an important role in the pathogenesis of VVS. NSE was abnormally elevated in this case, which is associated with a variant of neurogenic paraneoplastic syndrome. Alboni *et al* (16) and Benditt *et al* (17) observed that the level of noradrenaline was higher in patients prior to syncope compared with that in the control group, and the difference was statistically significant. In the clinical trials of Theodorakis *et al* (18), 83% (105/126) of patients had a positive response to clomipramine head-up tilt testing (clom-HUT), which is significantly higher compared with the 41% positive response rate to conventional HUT, indicating that the activity of 5-HT was enhanced in VVS patients, resulting in low blood pressure and sinus bradycardia. Thus, the neuroendocrine

Table I. Characteristics of 9 cases of small-cell lung cancer with episodic syncope.

Cases	Age, years /gender	Complaints	Stage	Location	Size, cm	Inducement	Chemotherapy	Radiation	Relapse therapy	Response	Refs.
Present case	61/M	Syncope twice	Limited T4N2M0	LH	6.8x6.0	Upright position	EC	-	-	PR	-
Case 1	64/M	Chest discomfort, syncope twice	Limited T4N2M0	LH	4.2x3.7	Walking, coughing	EC	-	+	CR	(3)
Case 2	57/M	Lightheadedness syncope once	Limited T2aN2M0	LUL	4.6x3.8	Bending forward	EP	+	-	PR	(4)
Case 3	57/M	Dyspnea, sweating syncope twice	Limited T2N2M0	LM	3.0x4.0	Upright position	EP	+	+	PR	(5)
Case 4	69/M	Recurrent syncopal episodes	Limited T4M0N0	LUL	5.6x4.3	Pain	CE	-	-	PR	(6)
Case 5	67/M	Chest pain, syncopal attack	Limited T1N2M0	LH	4.0x3.0	Upright position	CE	-	-	CR	(7)
Case 6	66/F	Syncopal attack	Limited T2bN2M0	LH	6.0x4.0	Upright position	CE	+	-	CR	(8)
Case 7	56/M	Chest pain, syncopal attack	Limited T4N2M0	LH	7.2x2.4	Standing and lying down	CE	+	-	PR	(9)
Case 8	64/M	Chest pain, syncopal attack	Limited T4N2M0	LH	8.0x6.0	After spirometry	CE	+	-	PR	(10)

LH, left hilum; LUL, left upper lobe; LM, left side of mediastinum; EC, etoposide + carboplatin; EP, etoposide + .

mechanism of SCLC clearly promoted the syncope to a certain extent. However, in the majority of the cases mentioned above, indicators of neurogenic paraneoplastic syndrome were not detected. When dealing with such cases, attention should be paid to changes in these indicators, which may be associated with the frequency of syncope.

The syncope symptoms of SCLC may be triggered by the upright position or severe coughing. Of the 8 patients reviewed in Table I, in 4 syncope was induced by the upright position, in 1 by coughing, and in 1 by bending forward. In the case reported in this study, all the syncope attacks occurred in the upright position.

The ventricular theory notes that it is easier for VVS to occur while standing upright when there is ~650 ml of blood pooled in the peripheral veins, accompanied by decreasing BP (19). According to the classic Bezold-Jarisch reflex theory, ventricular hypovolemia results in an increase in the sympathetic tone, which stimulates the 'empty chamber effect' and, in turn, activates the ventricular mechanoreceptors (C fibres). Then, with the impulse transmitted to the brainstem nucleus, the vagal tone is enhanced, leading to bradycardia and low cerebral perfusion (20). Emotional stress and intense coughing may also account for VVS (21). Therefore, the presence of these predisposing factors explains the characteristics of the onset of syncope to a certain extent, rather than its persistence.

In conclusion, tumour location, the neuroendocrine characteristics of SCLC, a change in body position and other factors, are all associated with syncope in SCLC. The precise role of those factors in triggering VVS remains unknown. Furthermore, based on our current understanding of the mechanisms underlying syncope in SCLC, a recommended diagnostic and treatment approach for unexplained syncope has been outlined.

Syncopal attack is a common complaint on admission, particularly for elderly patients. Other causes of syncope are usually neglected when cardiac and cerebral syncope are initially suspected. This may delay diagnosis and effective intervention and may result in patient death.

For any patients with a history of syncope, MRI, ECG, UCG and CTA are required to identify cerebral and cardiac diseases. The exclusion of glycopenia, epilepsy, carotid sinus syndrome, arrhythmia and steno-occlusive vascular disease and electrolyte disturbances may lead practitioners to consider VVS, particularly if lesions are found in the left hilum. HUT is recommended, if possible.

Preventing syncope episodes is crucial for treatment (22). Instructing the patients to avoid inducing factors may be beneficial. The sitting and semiprone position may be helpful during presyncope. If a syncope attack occurs, the Trendelenburg position may help to maintain the blood supply to the brain. In 9 reports reviewed herein, all the patients were evaluated as CR or PR according to the RECIST guidelines. Additionally, 7 patients experienced no relapse. In those cases, we consider that standard chemotherapy was crucial for preventing syncopal attacks in patients with SCLC. It appears to be more effective to use concurrent chemoradiotherapy for limitedstage disease. For extensive-stage SCLC, chemotherapy is the first choice of treatment. Etoposide plus cisplatin or carboplatin is the standard chemotherapeutic regimen for SCLC. A recent randomized phase III trial (23) suggested that irinotecan plus carboplatin in extensive-stage SCLC prolonged the overall survival compared with oral etoposide plus carboplatin, without compromising the quality of life (enrolled by NCCN in 2016).

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