Neurally Mediated Syncope Associated with Small Cell Lung Cancer: A Case Report and Review

Kenichiro Shimizu, Yutaka Yoshii, Sho Watanabe, Chiaki Hosoda, Masamichi Takagi, Toshimitsu Tominaga, Makoto Kawaishi and Kazuyoshi Kuwano

Abstract

We encountered a case of limited-disease small cell lung cancer with episodic syncope. The frequency of the syncopal attacks increased with the increase in the tumor size, thus a relationship was suspected to exist between the SCLC and syncope. Syncope was evaluated by history taking, 24-hour ECG monitoring, and coronary angiography. As orthostatic hypotension and cardiac disease could be excluded, we finally diagnosed this case as neurally mediated syncope. Serum tests for anti-Hu and anti-Yo antibodies were negative. A temporary pacemaker was inserted for sick sinus syndrome. This patient showed good response to the chemotherapy. No further syncopal attacks were observed after the second course of chemotherapy. Here, in addition we review four cases of SCLC with episodic syncope. Interestingly, in all cases, the tumor was located in the left hilum in close vicinity of the afferent vagal nerve (C-fibers) and mechano-receptor. Therefore, we thought that the mechanism underlying the syncope was mechano-receptor hypersensitivity.

Key words: small cell lung carcinoma, neurally mediated syncope, bradycardia, pacemaker, mechano-receptor hypersensitivity

Introduction

It has been reported that small cell lung cancer is rarely accompanied by episodic syncope. However, the mechanism underlying the occurrence of this type of syncope is still not well understood. We present a case and review four cases of SCLC with episodic syncope. Interestingly, in all cases, the tumor was located in the left hilum in close vicinity to the afferent vagal nerve (C-fibers) and mechano-receptor. Therefore, we thought that the mechanism underlying the syncope was mechano-receptor hypersensitivity.

Case Report

A 64-year-old man with a medical history of surgery for gastric cancer, was admitted to our hospital for further evaluation of a left hilar mass and episodic syncope. The first syncope occurred when the patient was resting in bed at home; it precipitated chest discomfort and lasted for a few seconds. He visited our hospital the following day. Since lung cancer was suspected on chest X-ray, he was admitted for further evaluation.

On admission, physical examination revealed no significant abnormalities other than mild bradycardia (HR 51 beats/min). Both the electrocardiogram (ECG) and ultrasonic cardiology (UCG) were normal. Laboratory testing revealed mild anemia and elevated serum tumor marker levels (NSE 32.4 ng/mL, proGRP 420 pg/mL). Contrast-enhanced chest CT (Fig. 1a, b) showed a mass measuring 8.0 × 6.0 cm in the left hilum, invading the left main pulmonary artery and close to the aortic arch. Fiberoptic bronchoscopy showed a tumor obstructing the left upper bronchus, and transbronchial biopsy (TBB) revealed the diagnosis of small cell lung cancer. There was no evidence of metastasis. Therefore, the diagnosis was made of limited disease small cell lung cancer (cT4N2M0, IIIB).

On day 9 of admission, after spirometry, the patient de-
He developed a second episode of syncope. ECG monitoring (Fig. 1c) revealed severe bradycardia (heart rate 25 beats/min) and hypotension, consistent with sick sinus syndrome. He was immediately given a single dose of atropine 0.5 mg i.v. and started on continuous intravenous infusion of dopamine and followed by isoproterenol. Although his performance status (PS) was grade 3, he was started on combined chemotherapy with carboplatin plus etoposide (VP-16) on day 14 of admission (CBDCA at AUC=5 on day 1 plus VP-16 at 80 mg/m² on days 1-3), based on the suspected existence of a relationship between the recurrent syncope and progression of SCLC. It was necessary to delay the second course of chemotherapy due to the development of febrile neutropenia. With increasing tumor size, the patient developed a third attack of syncope when resting in bed. At this time, UCG and coronary angiography (CAG) were performed, and then a pacemaker was positioned. UCG did not reveal any abnormality, and CAG revealed no significant stenosis of the coronary artery or coronary spasm on acetylcholine provocation. Therefore, after the exclusion of orthostatic hypotension and cardiac syncope, we finally made the diagnosis of neurally mediated syncope. Serum tests for anti-Hu and anti-Yo antibodies (1), characteristically positive in cases of neurogenic paraneoplastic syndrome, were negative. The patient showed partial response (PR) after a total of four courses of chemotherapy followed by irradiation (2.5 Gy once daily for 20 days; totally 50 Gy). The pacemaker was removed because of cessation of the syncopal attacks.

**Discussion**

Episodic syncope associated with SCLC is rare. There are only four case reports, including the present case. We summarized the characteristic features of all four cases in Table 1; all were characterized by limited disease SCLC, left hilar location of the tumor, good response to systemic chemotherapy, and disappearance of syncope after chemotherapy.

SCLC is well known to be frequently associated with a variety of neurogenic paraneoplastic syndromes, such as myasthenia gravis (MG), Lambert-Eaton myasthenic syndrome (LEMS), and limbic encephalitis. On the other hand, the association of episodic syncope with SCLC is not well understood. Previous reports (2-4) have speculated that syncope in patients with SCLC may also represent a component of the neurogenic paraneoplastic syndrome. However, there are some discrepancies. First, autoantibodies were not detected in any of the cases. Secondly, if syncope were a component of the paraneoplastic syndrome, then it should occur with the tumor located anywhere in the lung. However, in all four cases, the tumor was located nowhere other than at the left hilum. Thirdly, the syncope disappeared early and could no longer be induced during the head-up tilt test after the initiation of systemic chemotherapy (4) even though residual tumor antigens were still present in the body. Interestingly, in all of the cases, the tumor was located in the left hilum, near the left vagus nerve. Therefore, it was thought that this condition may represent a location-dependent syndrome.
rather than a component of the neurogenic paraneoplastic syndrome. As there are only four case reports of episodic syncope associated with SCLC, further accumulation of cases is necessary to clarify the mechanism of development of syncope in patients with SCLC.

Three of the reported cases (2-4) of episodic syncope associated with lung cancer were patients with small cell lung cancer; while one case (5) had large cell lung cancer; although in this case also, the tumor was located in the left hilum. Tumor at this location presumably stimulates the left vagus nerve, especially afferent vagal nerve (C-fiber) and mechano-receptor. It is believed that an increase in afferent neural activity produces a centrally mediated paradoxic decrease in heart rate and peripheral vasodilatation, resulting in neurally mediated syncope (6, 7). Moreover, loss of stimulation of the left vagal nerve by a reduction of the tumor size after chemotherapy might effectively control the syncope.

**Conclusion**

We present a case of small cell lung cancer presenting with episodic neurally mediated syncope, who required a temporary pacemaker. Treatment should be initiated promptly even in patients with a poor general condition, because it would be expected to effectively control the neurally mediated syncopal attacks.

The authors state that they have no Conflict of Interest (COI).

**References**


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