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【 CASE REPORT 】

# Glossopharyngeal Neuralgia with Syncope Caused by Recurrence of Esophageal Squamous Cell Carcinoma

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**Abstract:**

We herein report a case of glossopharyngeal neuralgia with repeated syncope caused by the recurrence of esophageal carcinoma. The typical symptoms of glossopharyngeal neuralgia are paroxysmal, stabbing, electric shock-like pain in the pharynx and/or base of the tongue on swallowing and talking. In addition, syncope can also be caused by glossopharyngeal neuralgia. The diagnosis of glossopharyngeal neuralgia is not always easy because of its rarity. In the present case, we suspected that repeated syncope was caused by glossopharyngeal neuralgia due to the recurrence of esophageal carcinoma. Concurrent chemoradiation therapy was effective in reducing the tumor size, which resulted in the complete resolution of the symptoms.

**Key words:** glossopharyngeal neuralgia, esophageal carcinoma, syncope

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## Introduction

Syncope is caused by a wide variety of disorders (1). Direct invasion of primary neck carcinoma and metastatic lymphadenopathy to the glossopharyngeal nerve or vascular compression of the glossopharyngeal nerve can cause glossopharyngeal neuralgia with syncope (2). Glossopharyngeal neuralgia occurs in approximately 0.4-0.8 per 100,000 persons per year (2, 3), and the frequency of glossopharyngeal neuralgia due to head and neck tumors overall is reported to be approximately 0.04-0.15% (4, 5). The typical symptoms are paroxysmal, stabbing, electric shock-like pain in the pharynx and/or base of the tongue on swallowing and talking (6). However, the diagnosis is not always easy because the disease is rare (6).

We herein report a case of repeated syncope caused by tumor invasion to the right glossopharyngeal nerve from metastatic lymphadenopathy of esophageal squamous cell carcinoma.

## Case Report

A 78-year-old Japanese man was referred to our hospital because of repeated syncopal attacks. He had been diagnosed with early esophageal squamous carcinoma three years earlier, which was located 25-28 cm from the superior incisor, and been treated with endoscopic submucosal dissection (ESD). A histopathological analysis of the resected specimen suggested that the resection was non-curative because the moderately differentiated squamous cell carcinoma showed invasion into the deep submucosal layer as well as lympho-vascular invasion (pT1b-SM2, ly2, v2, pHM0, pVM0, pR0: by the Japanese classification of esophageal cancer version 11). However, additional surgical esophagectomy or chemoradiotherapy had not been attempted, per the patient's wishes. Three years after the endoscopic treatment, the patient noticed a left cervical mass and simultaneously experienced repeated syncopal attacks. His laboratory tests, electrocardiogram, ultrasonic cardiogram and head computed tomography (CT) scans did not show any suspicious findings that might lead to repeated syncope. He was therefore admitted to our hospital for a further evaluation.

Upon admission, his tumor marker levels were found to be slightly elevated. His squamous cell carcinoma-associated antigen (SCC) and cytokeratin 19 fragment (CYFRA) levels were 2.0 ng/mL (normal range: 0-1.5 ng/mL) and 28.5 ng/mL (normal range: 0-3.5 ng/mL), respectively. Contrast-

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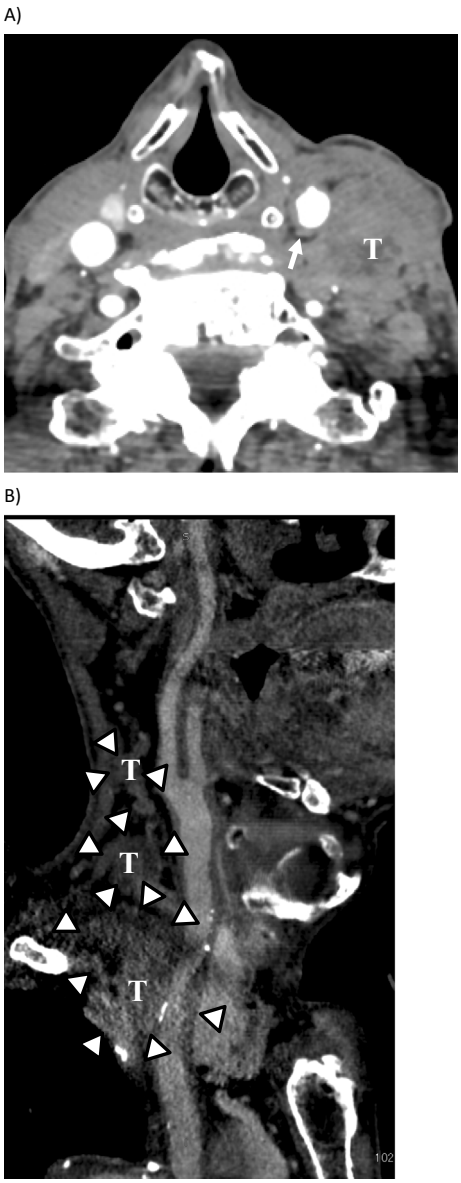


**Figure 1. Contrast-enhanced CT showed a tumor (T) in the left parapharyngeal space infiltrating the left common carotid artery (arrow). (A: axial section, B: sagittal section)**

enhanced CT demonstrated swollen left parapharyngeal lymph nodes with up to 35×58 mm infiltration around the left common carotid artery (Fig. 1). The right common carotid artery also showed narrowing, but sufficient blood flow was preserved. In addition, narrowing of the right common carotid artery had been observed five years earlier, but no syncopal attacks had occurred at that point. The head and chest CT findings showed no other abnormal findings. There were also no regional lymph node metastases. Upper esophagogastroduodenoscopy did not show any findings suggestive of local recurrence of esophageal cancer. We later found that the upright tilt-table test showed a decrease in the arterial blood pressure and heart rate with reproduction of the symptoms. Therefore, the right common carotid artery narrowing seemed to be unrelated to the syncope, and neurogenic syncope was instead the suspected cause of his repeated syncope.

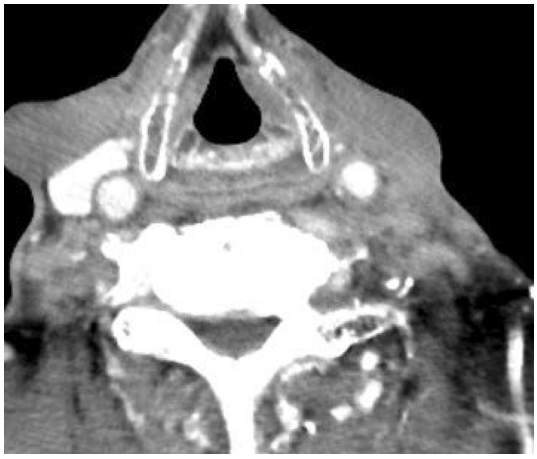

**Figure 2. Follow-up CT after concurrent chemoradiation therapy for two months showed regression of the metastatic lymph node.**

After we carefully checked his symptoms again, we found that the patient always experienced pharyngeal pain before provoking syncope. The pain was severe, shooting and unilateral. This met the diagnostic criteria of glossopharyngeal neuralgia according to the International Headache Society (6). The repeated syncope might have been induced by this glossopharyngeal neuralgia. The frequency of syncope increased with the growth of the parapharyngeal lymph node. Therefore, we considered the pharyngeal pain to have been derived from the direct stimulation of the glossopharyngeal nerve, with the malignancy-related glossopharyngeal neuralgia subsequently causing neural-mediated syncope. In addition, the symptomatic glossopharyngeal neuralgia with syncope was deemed to have been caused by the recurrence of esophageal squamous cell carcinoma.

However, recurrent tumor was not histopathologically confirmed because the mass was located near the great vessels, and biopsy approaches, such as a needle and excisional biopsy, were considered difficult and risky. Surgery was not indicated because of local expansion. A trial of a sympathomimetic drug was not effective. However, we believed that reducing the tumor size would improve the symptoms. Therefore, concurrent chemoradiation therapy (cCRT) was commenced. The patient received 2 courses of systemic chemotherapy with nedaplatin and 5-fluorouracil and a total of 60 Gy of irradiation concomitantly. After the completion of cCRT, the tumor regressed, and the episodes of glossopharyngeal neuralgia with syncope resolved completely (Fig. 2, 3). No recurrences of the tumor or glossopharyngeal neuralgia with syncope have been observed in the past 22 months.

## Discussion

Reflex cardiovascular syndromes induced by cervical malignant tumors are categorized into the following three types: carotid sinus syndrome, glossopharyngeal neuralgia-asystole syndrome and parapharyngeal space lesions

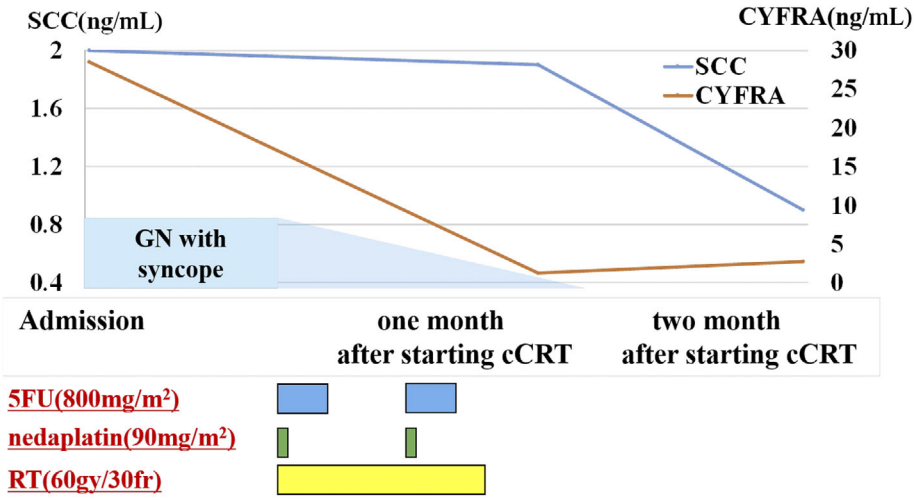


**Figure 3.** **The clinical course of the case. After concurrent chemoradiation therapy, the tumor regressed and episodes of glossopharyngeal neuralgia with syncope gradually became less frequent and finally resolved completely.**

syncope-syndrome (7). In the present case, the patient always experienced pharyngeal pain before syncope. Therefore, we considered that this case belonged to the glossopharyngeal neuralgia-asystole syndrome category. The spread of neck cancer or lymphoma around the glossopharyngeal nerve and vascular/stylohyoid ligament compression of the glossopharyngeal nerve can induce glossopharyngeal neuralgia with syncope (6).

Two mechanisms have been postulated to cause syncope in cases of neck carcinoma (4, 8). First, the tumor directly stimulates the peripheral branches of the glossopharyngeal nerve. Afferent glossopharyngeal stimulation proceeds to the brainstem centers in the caudal nucleus of the solitary tract. Interneurons then activate the efferent fibers, resulting in stimulation of the parasympathetic systems, leading to bradycardia (4, 8). Second, afferent glossopharyngeal stimulation proceeds to brainstem centers in the spinal nucleus of trigeminus. This has an inhibitory effect on vasomotor centers, which leads to peripheral vasodilation and pronounced hypotension (4, 8). Carbamazepine is a proposed medical agent for the treatment of glossopharyngeal neuralgia. It can control glossopharyngeal neuralgia by its inhibitory effect on the brain stem reflex activity (9, 10). However, it is sometimes ineffective, and patients become tolerant after prolonged use. Furthermore, the medication must be administered permanently (11). In addition, the prolonged use of the agent may cause adverse effects, such as eruption, drowsiness, dizziness, nausea and vomiting. Another treatment option is pacemaker implantation, but it cannot prevent vasodepressor response syncope and glossopharyngeal neuralgia (12-14). We considered that reduction of the tumor was the only fundamental treatment that could reduce glossopharyngeal neuralgia with syncope in the present case. In such cases, surgical resection may be the best option (15, 16). However, surgical resection was considered too risky because of the location in the present case.

As an alternative to surgery, several case reports have shown the complete resolution of symptoms after chemotherapy or radiotherapy in cases of lymphoma and esophageal squamous cell carcinoma (17, 18). Ishida et al. (19) reported that the overall tumor response and complete response rates after cCRT were 68.3% and 15% in esophageal cancer with invasion to surrounding organs and/or metastasis. A certain number of patients who respond to this treatment can be expected to achieve improvement in their symptoms. Therefore, we decided to commence cCRT. Regarding the cCRT regimen, we considered the use of cisplatin to be risky in the present case because of his advanced age, impaired renal function (low creatinine clearance of 47 mL/min/1.73 $m^2$) and poor performance status. Nedaplatin has less nephrotoxicity, gastrointestinal toxicity and neurotoxicity than cisplatin. Furthermore, the efficacy of 5-FU and nedaplatin with concurrent radiotherapy is comparable to that of 5-FU and cisplatin (20, 21). Therefore, we used nedaplatin instead of cisplatin. As a result, our patient had a good prognosis with no recurrent syncope after cCRT.

In conclusion, we present a case of glossopharyngeal neuralgia with syncope caused by recurrence of esophageal squamous cell carcinoma. cCRT was effective and reduced the tumor size, which resulted in complete resolution of symptoms.

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

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