Second-line chemotherapy for refractory small cell neuroendocrine carcinoma of the esophagus that relapsed after complete remission with irinotecan plus cisplatin therapy: Case report and review of the literature

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Abstract. Small cell esophageal carcinoma is a type of small cell neuroendocrine carcinoma (SCNEC). SCNEC follows an aggressive clinical course and has a poor prognosis despite multidisciplinary therapies. A standard therapeutic strategy, including surgery, radiation and first-/second-line chemotherapy, has not yet been established for SCNEC. We present a case of SCNEC of the esophagus. A 66-year-old male with SCNEC as extensive disease was treated with 60 mg/m^2 cisplatin on day 1 plus 60 mg/m^2 irinotecan on days 1, 8 and 15 every 4 weeks (IP) with successful complete remission. After the sixth course of IP, increasing pro-gastrin-releasing peptide (ProGRP) and nonspecific enolase (NSE) levels and intense fluorodeoxyglucose (FDG) avidity in a lymph node around the celiac artery (SUV_{max}, 8.3) indicated a refractory relapse of the disease. The patient was treated with three courses of amrubicin (AMR, 35 mg/m^2) administered intravenously for 3 consecutive days every 3 weeks as a second-line chemotherapy. The ProGRP and NSE levels returned to the normal range 1 month after the initiation of second-line chemotherapy. However, the ProGRP and NSE levels were elevated after the third course of AMR, and PET-CT revealed progressive disease with liver metastasis and extended lymph node metastasis. As the patient remained asymptomatic, paclitaxel (100 mg/m^2) was started as third-line chemotherapy. Patients with SCNEC of the esophagus with extensive disease should be treated with aggressive chemotherapy rather than surgery or radiation monotherapy. In the present case, tumor markers such as ProGRP and NSE were predictive of relapse and PET-CT was used to detect relapse. Further research is required to identify and exploit promising agents for resistant SCNEC.

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Introduction

More than 300 cases of small cell esophageal carcinoma have been reported since the initial case report by McKeown in 1952 (1). Small cell neuroendocrine carcinoma (SCNEC) is a rare disease with aggressive and malignant biological behavior and a poor prognosis. SCNEC accounts for 1.0 to 2.8% of all esophageal cancers (2,3). A new classification of neuroendocrine tumors that included SCNEC was introduced by the World Health Organization (WHO) in 2010 (4). This new classification distinguishes between well- and poorly differentiated neuroendocrine tumors in a different manner than the 1963 classification by Sandler and Williams, and the 2000 classification by WHO (5-7). Small and large cell esophageal carcinomas are classified as neuroendocrine carcinomas (NECs) of proliferative activity grade 3 (Ki-67 >20%). Although SCNEC is a highly proliferative carcinoma, a standard therapeutic strategy has not yet been developed. A multidisciplinary treatment approach consisting of resection, chemotherapy and radiation therapy is recommended for the treatment of extrapulmonary small cell carcinoma according to the National Comprehensive Cancer Network (NCCN) guidelines for small cell lung cancer. In the present study, we review previous studies and clinical trials of treatments for NECs resistant to chemotherapy.

Case report

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A 66-year-old male was referred to our hospital in October 2009 with an initial diagnosis of esophageal cancer based on

the results of gastrointestinal endoscopy. The patient had not experienced dysphagia, weight loss or retrosternal/epigastric pain. The patient had a history of tobacco and alcohol use. There was no personal or family history of malignancy. A physical examination revealed no abnormalities. A routine complete blood count revealed normochromic anemia with a hemoglobin level of 10.2 g/dl. Blood chemistry findings revealed hypoalbuminemia (albumin, 3.2 g/dl). Barium studies and endoscopic examination of the upper gastrointestinal tract revealed a type 2 tumor in the middle of the esophagus (Fig. 1A and B). The tumor contained a deep central ulceration 4.5 cm in length. Hematoxylin-eosin (HE) and immunohistochemical staining were performed on biopsy samples. Microscopic examination of endoscopic biopsy specimens revealed a small cell carcinoma that had invaded into the submucosal region. The tumor cells showed a high nuclear-cytoplasmic ratio, hyperchromic nuclei and absent or inconspicuous nucleoli, which are typical features of small cell lung carcinoma (SCLC; Fig. 2A). Tumor cells were positive for AE1/AE3, synaptophysin (Fig. 2B) and CD56. Chromogranin-positive cells were scattered. More than 40% of tumor cells were positive for Ki-67 (Fig. 2C). The pathological diagnosis of the tumor was NEC, G3, small cell type. The patient was finally diagnosed with SCNEC of the esophagus. A contrast-enhanced computed tomography (CT) scan of the chest and abdomen revealed an area of poorly enhancing esophageal wall thickening, which was 4.5 cm long, concomitant with enlarged lymph nodes (Fig. 1C). Fluorodeoxyglucose positron emission tomography/CT (FDG PET-CT) revealed an ^{18}F-FDG-accumulated primary lesion and multiple lymph nodes around the mediastinal locoregional lesion and the celiac artery with maximal standardized uptake value (SUV_{max}) of 3.0-9.0. The clinical stage was classified as cT3N2M0, stage IIIB [2010 Seventh Edition of the American Joint Committee on Cancer (AJCC)/International Union Against Cancer (UICC)] (8,9), and it was considered to be extensive disease according to the Veterans' Administration Lung Study Group (VALSG) Staging System used for small cell lung cancer (10). Laboratory tests revealed an elevated level of serum progastrin-releasing peptide (ProGRP, 105 pg/ml; normal range, <81.0 pg/ml) and nonspecific enolase (NSE; 21.1 ng/ml; normal range, <16.3 ng/ml). The serum carcinoembryonic antigen (CEA) and squamous cell carcinoma antigen (SCC) levels were within normal limits. The patient was in good condition with an Eastern Cooperative Oncology Group performance status of 0.

Combination chemotherapy consisting of 60 mg/m^2 cisplatin on day 1 plus 60 mg/m^2 irinotecan administered intravenously on days 1, 8 and 15 was administered every 4 weeks (IP) from Dec 2010 until Aug 2011. During the first chemotherapy course, the patient developed bacterial pneumonia with neutropenia. Therefore, the total dose of cisplatin was reduced by 20% for the remaining 5 courses. After the third course of IP, the primary lesion disappeared and multiple lymph nodes that had been previously enlarged were reduced to normal size, as indicated by GI endoscopy and PET-CT. No cancer cells were observed in an endoscopic biopsy specimen, indicating a positive therapeutic response and complete remission of the tumor. However, lymph nodes around the celiac artery increased in size again in October 2011 immediately following cessation of the sixth course of IP. These enlarged lymph nodes were considered to indicate refractory relapse cancer. The ProGRP and NSE levels increased further. The axial PET-CT image revealed intense FDG avidity in lymph nodes around the celiac artery with an SUV_{max} of 8.3. The patient was treated with amrubicin (AMR, 35 mg/m^2) administered intravenously for 3 consecutive days every 3 weeks. In the first round of AMR therapy, the patient experienced febrile neutropenia that was treated with ciprofloxacin. Hence, the total dose of AMR was reduced by 20% for the remaining 2 courses. Although the ProGRP and NSE levels returned to normal 1 month after the initiation of AMR chemotherapy, they were elevated after the third course of AMR, and PET-CT revealed progressive disease with liver metastasis and expanded lymph node metastasis. As the patient remained asymptomatic, paclitaxel (100 mg/m^2) was started as third-line chemotherapy.

Extrapulmonary SCNECs are relatively rare tumors that occur in almost every organ, including the cervix, esophagus, pharynx, larynx, lymph node, pancreas, colon and rectum. According to the epidemiological data, the prevalence and incidence of gastroentero-pancreatic neuroendocrine tumors have been increasing, which is likely due to improved detection methods (11). Although certain extrapulmonary SCNECs have slow progressive behavior, most are aggressive and have a poor prognosis despite various multidisciplinary treatments. In particular, gastrointestinal SCNECs, including esophageal SCNECs, have a worse prognosis compared with tumors in other sites (12).

In the present study, we reviewed the literature regarding characteristics of SCNEC. We searched PubMed and Ichushi-Web with a combination of three terms, 'small cell carcinoma', 'neuroendocrine carcinoma' and 'esophagus', for studies published in or after 2000. Our search yielded 229 reports of SCNEC, from which we extracted the data on diagnosis, age, gender, disease stage, treatment and survival time. The data (including the present case) are summarized in Table I. The median age was 64 years (interquartile range, 23-90 years) and the majority (73%) of the patients were male.

Macroscopic tumor characteristics and clinical stage. Most esophageal SCNECs occur in the middle (50%) or lower (42%) sites of the esophagus, as shown in Table I. The average tumor length was 6.5 cm (±2.3 cm) and 66% (88/133) of the tumors were longer than 5 cm. The most frequent gross appearance of SCNEC was type 2 localized ulcerated type, which accounted for 57% (55/96) of cases. According to the VALSG criteria, 53% (121 of 229) of all cases had limited disease and 47% (108 of 229) had extensive disease (ED).

Histology and immunohistochemistry. In the 21st century, the WHO classification for neuroendocrine tumors (NETs) has been revised twice. The WHO 2000 classification focused on tumor stage, including lymph node or distant metastasis, while the WHO 2010 classification is more practical and reflects clinical prognosis. SCNEC is to be included in NEC for high grade (G3) moderately to poorly differentiated neuroendocrine neoplasms. In addition, extrapulmonary SCNECs, including SCNECs of the esophagus, are indistinguishable from SCLC in histological and immunohistochemical features (13,14). Due to their histological similarity, protocols for SCLC have been recommended for the diagnosis of extrapulmonary SCNEC (15). Accurate histological diagnosis is critical as

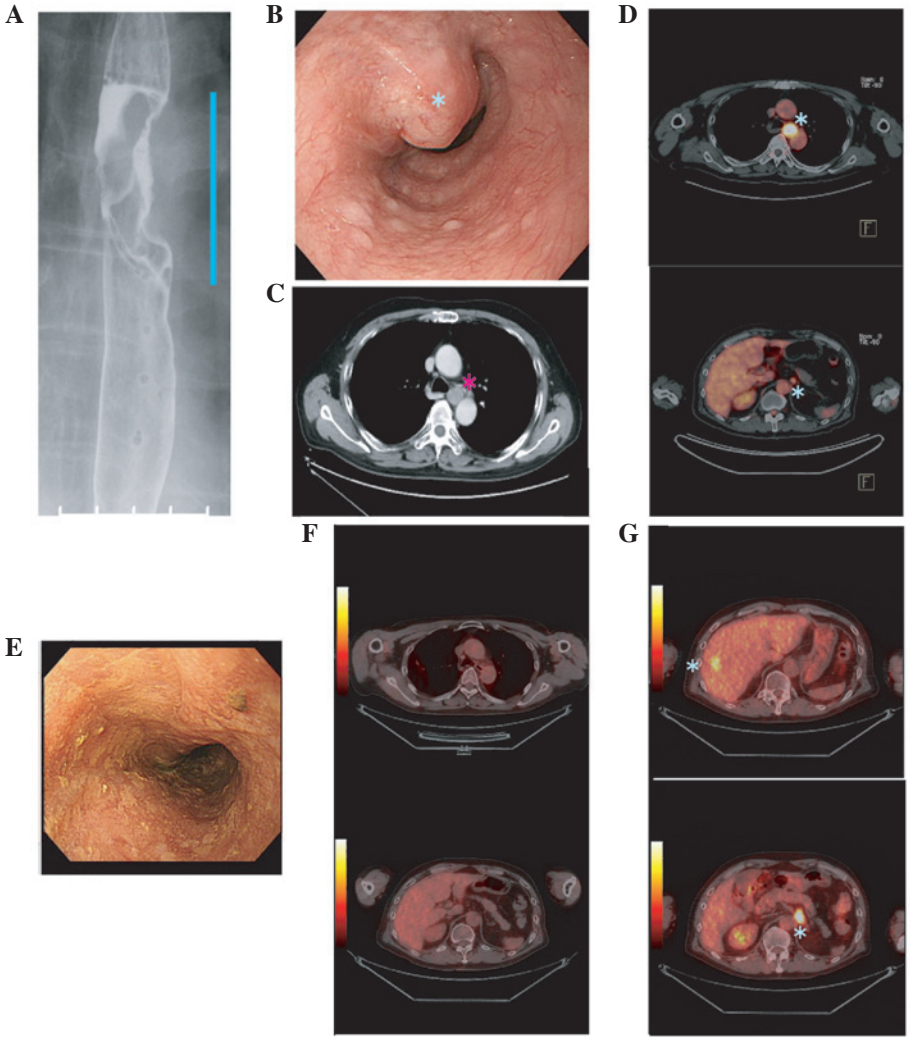

Figure 1. A 66-year-old male. (A-D) pretreatment, (E-G) posttreatment. (A) A type 2 tumor with a deep central ulceration 4.5 cm in length was present in the middle of the esophagus as shown by the esophagogram. (B) Gastrointestinal endoscopy revealed that the type 2 tumor occupied half of the circumference of the esophagus. (C) A CT scan of the chest and abdomen revealed a 4.5-cm lesion in which wall thickening was present concomitant with enlarged lymph nodes. (D) PET-CT revealed FDG accumulation in the primary lesion and multiple lymph nodes around the mediastinal locoregional lesion and the celiac artery at diagnosis. (E) Endoscopy revealed no residual tumor after treatment with IP chemotherapy. (F) PET-CT demonstrated complete radiological remission of the esophageal tumor and lymph nodes after 3 months of chemotherapy. (G) After 3 courses of AMR chemotherapy, PET-CT revealed liver and lymph node metastasis. CT, computed tomography; PET, positron emission tomography; FDG, fluorodeoxyglucose; AMR, amrubicin.

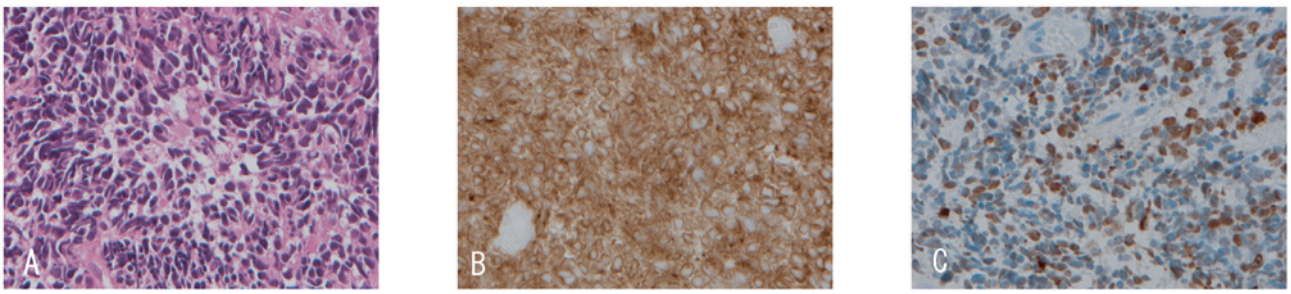

Figure 2. Endoscopic biopsy specimens. (A) The tumor cells have scant cytoplasm, hyperchromatic nuclei and absent or inconspicuous nucleoli (hematoxylin-eosin stain; original magnification, x200). (B) The tumor cells show positive staining for synaptophysin (original magnification, x400). (C) More than 40% of the nuclei are positive for Ki-67 (original magnification, x400).

systemic chemotherapy recommended for SCNEC differs from therapies for squamous cell carcinoma or adenocarcinoma of the esophagus. To diagnose the tumor as SCNEC, it is essential to identify typical small cell carcinoma histology and immunohistochemical evidence of epithelial differentiation. Although positive staining for neuroendocrine markers is not necessary, it makes a supplementary contribution to the diagnosis. Li *et al* reported that the incidence for positive

Table I. Patient characteristics and treatment course for the 9 cases of small cell carcinoma of the esophagus that relapsed after complete remission with chemotherapy or resection by surgery in the literature between 2000 and 2011.

Case/ (Ref.)	Gender	Age (years)	Type	Location	Tumor size (mm)	VALSG stage	Sensitive relapse	Refractory relapse	CT regimen	Radiotherapy (Gy)	Treatment course	Survival time after recurrence (months)	Survival time (months)	Outcome
1[a]	Male	66	2	Mt	30	ED		1	IPx6, AMRx3, TXLx1	-	CT, CT, CT	>6	17	Alive
2 (16)	Male	53	NA	MtLt	NA	ED	1		EPx4, sur, RT, EPx7, topotecan/paclitaxelx1, CPT-11/paclitaxelx1	40	CT, sur, RT, CT, CT, CT	NA	44	Deceased
3 (17)	Male	66	3	MtLt	NA	ED		1	IPx4, RT/TXL, CBDCA/VP16	60	CT, CRT, CT	>9	16	Alive
4 (18)	Male	59	2	UtMt	60	ED		1	IPx6, CBDCA, VP16x3	-	CT-CT	6	18	Deceased
5 (19)	Male	53	1	MtLt	100	ED	1		CDDP, etoposide, FPx2, DOC, IP	45	CCRT, sur, CT, hepatectomy	>48	56	Alive
6 (20)	Male	65	2	Mt	NA	ED		1	CDDP/5FU, CPT-11, GEM, TXL	60	CCRT, CT, CT	>10	18	Alive
7 (21)	Male	59	3	Lt	90	ED		1	FPx10, ETPx6, ETP/CPA/EPIx3, FPx4/RT	-	CT, CT, CT, CCRT	12	24	Deceased
8 (22)	Male	65	NA	Lt	95	ED		1	PVP/CAV	60	CRT, sur, CT	NA	17	Deceased
9 (22)	Female	61	2	Mt	58	LD	1		PVP/CEV, 5FU, CBDCA	-	CT, sur, CT	12	21	Deceased

VALSG, Veterans' Administration Lung Study Group; CT, chemotherapy; CRT, chemoradiation therapy; CCRT, concurrent chemoradiation therapy; ED, extensive disease; LD, localized disease; Lt, lower thoracic esophagus; Mt, mid-thoracic esophagus; NA, not available; RT, radiation therapy; sur, surgery; Ut, upper thoracic esophagus; AMR, amrubicin; CAV, cyclophosphamide + Adriamycin + vincristine; CBDCA, carboplatin; CEV, cyclophosphamide + epirubicin + vincristine; CPA, cyclophosphamide; DOC, docetaxel; EP, etoposide + CDDP; EPI, epirubicin; ETP, etoposide; FP, 5FU + CDDP; GEM, gemcitabine; IP, irinotecan + CDDP; PVP, cisplatin + etoposide; TXL, taxol. [a]Present study.

immunohistochemical reactivity for CK8, synaptophysin, NSE and CD56 in gastrointestinal SCNEC was >90% and that these markers were useful in diagnosis (14,23), whereas Yun *et al* reported that the percentages of SCNEC samples with positive immunoreactivity were: Syn, 95.2%; CD56, 76.2%; TTF-1, 71.4%; NSE, 61.9%; CgA, 61.9%; CK, 57.1%; EMA, 61.9%; and S100, 19.0% (14). A multivariate analysis by Shia *et al* identified the following three factors as having an adverse impact on 2-year disease-specific survival: the absence of an associated adenocarcinoma component (P=0.04), the presence of synaptophysin staining (P=0.05) and high disease stage (P<0.0001) (24). The present case has all three of these factors; thus, a poor prognosis may be predicted.

Imaging for diagnosis and the evaluation of the response to treatment. As reported by Howard *et al* (12), little information has been reported regarding the CT findings of extrapulmonary SCNEC. The use of high-resolution CT is the current standard approach to assess tumor spreading. However, PET-CT may be useful for both staging and restaging by detecting new lesions as SCNEC is typically ^{18}F-FDG avid (12,25). In the present case, the results of PET-CT influenced the decision to initiate second-line chemotherapy after disease recurrence was detected, concomitant with the elevation of NSE and ProGRP levels. Careful evaluation is necessary as SCNEC tends to recur repeatedly at distant sites, including the brain. It remains to be determined if PET-CT will lead to improved patient outcome in restaging after treatment. Further investigations are needed to confirm the benefit and cost effectiveness of PET-CT compared with conventional imaging techniques such as contrast-enhanced CT.

Treatments

Surgery. Surgery is one of the mainstay treatments for neuroendocrine tumors (NETs) (G1, G2), with the exception of cases with distant metastasis, whereas there is no definitive evidence that surgery is optimal for NEC (G3), including esophageal disease (11). However, certain studies advocate surgery as a treatment for SCNEC cases with limited disease, but not with ED, due to the possibility of a benefit to long-term survival (2). The outcome for SCNEC treated with surgery alone is extremely poor due to a high likelihood of disease recurrence, even following complete resection; therefore, chemotherapy and chemoradiation before or after surgery may be critical for improved survival.

Radiotherapy. Radiotherapy alone is insufficient to improve the survival of SCNEC patients. Rather, radiotherapy has been successfully used to treat bone and brain metastases. Radioembolization using Yttrium-90 microspheres has been revealed as an optional treatment for tumor control of NET with liver metastasis (25).

Chemotherapy. The therapeutic strategies for slowly progressive NET (G1, G2) and rapidly progressive NEC (G3) are fundamentally different. NCCN guidelines recommend: i) a watch-and-wait approach every 3 to 6 months until the disease progresses; ii) enrollment in a clinical trial; or iii) the administration of octreotide, which is a somatostatin analog and a biotherapeutic agent (26). In February 2011, the New England Journal of Medicine published reports that everolimus and sunitinib demonstrated significant clinical benefit in a randomized phase 3 trial for the treatment of advanced pancreatic neuroendocrine tumors (26,27). However, according to SCLC guidelines, systemic chemotherapy is recommended for the treatment of NEC. A regimen of etoposide and cisplatin (EP) is most frequently used in patients with SCLC. Furthermore, EP plus concurrent thoracic radiotherapy are recommended for SCLC with limited disease (15). A randomized phase 3 trial for SCLC with extensive disease in Japan demonstrated a significant difference in survival between patients treated with IP and EP (28). Unfortunately, two subsequent phase 3 trials performed in the USA found no benefit in the use of IP therapy instead of EP therapy (29,30). We selected the IP regimen for first-line therapy in the present case (28).

Most patients eventually relapse after initial chemotherapy and require second-line chemotherapy. As shown in Table I, only a few studies published between 2000 and 2011 have reported the treatment course for patients with SCNEC that relapsed after a complete remission with chemotherapy or resection by surgery. In general, the prognosis at relapse is extremely poor, and the response to second-line chemotherapy tends to be limited. There are occasions when this rule does not apply. Several phase 2 studies have demonstrated that single-agent amrubicin (AMR) had promising effects on patients with refractory SCLC (31,32). Results from these studies showed overall response rates of 21.3 to 53% and median survival periods of 5.7 to 10.3 months in refractory SCLC. AMR is a promising agent for second-line therapy in patients with platinum-refractory SCLC. Furthermore, Asayama *et al* have reported the achievement of an objective response in two of three patients with refractory or recurrent SCNEC treated with AMR as a second- or third-line therapy (35).

As candidates for single-agent, second-line chemotherapy in SCLC, etoposide, topotecan, paclitaxel, gemcitabine, pemetrexed and picoplatin may be considered in addition to AMR. Although etoposide, pemetrexed and gemcitabine failed to demonstrate survival benefits, better response rates were achieved compared with the response rates of 47% for irinotecan and 29% for paclitaxel (36). Moreover, clinical trials for bortezomib, bendamustine, sunitinib, rebeccamycin analog BI 2536, Hsp90 inhibitor, STA-9090, BIBF 1120, ADI-PEG 20, chloroquinoxaline sulfonamide, FR901228 and NK012 are currently underway throughout the world.

The candidates for combination second-line chemotherapy in SCLC include cisplatin + etoposide, cisplatin + irinotecan, carboplatin + irinotecan, cisplatin + etoposide + irinotecan, carboplatin + paclitaxel, paclitaxel + everolimus, pasireotideLAR + topotecan, paclitaxel + gemcitabine, topotecan + bevacizumab and vorinostat + topotecan. The response rates for these treatments have varied, and further investigations are necessary to identify their effectiveness for chemotherapy-resistant SCLC. Molecular-targeted agents, including imatinib, bevacizumab, cediranib, sorafenib and gefitinib, have not been promising treatments for SCLC (36). The development of various chemotherapeutic agents for NEC is expected.

Conclusion

Patients with SCNEC of the esophagus with ED should be treated with aggressive chemotherapy rather than surgery or radiation monotherapy. In this case, tumor markers such as

ProGRP, NSE and PET-CT detected disease relapse. Further research may be required to exploit the promising agents for treatment of chemotherapy-resistant SCNEC.

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