A CLINICAL CASE REPORT ON THE TREATMENT OF SMALL CELL CARCINOMA OF THE ESOPHAGUS AT HANOI MEDICAL UNIVERSITY HOSPITAL

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Small cell neuroendocrine carcinoma of the esophagus (SCNEC) is a rare and highly aggressive histological subtype that requires a multimodal treatment approach, including chemotherapy, surgery, and radiotherapy. Among these options, concurrent chemoradiotherapy with etoposide and cisplatin (EP) regimen is an effective treatment choice for patients with locoregional disease. We report the case of a 61-year-old male patient diagnosed with stage cT4bN2M0 SCNEC who received radiotherapy combined with EP chemotherapy. Following treatment, endoscopic evaluation revealed marked tumor regression, leaving only a residual ulcer scar, and tumor markers returned to normal levels, indicating a complete clinical response (CCR). To date, follow-up has shown no evidence of local recurrence or distant metastasis, with a progression-free survival (PFS) of 24 months. This case demonstrates the efficacy and safety of combined radiotherapy and EP chemotherapy in locoregional SCNEC, highlighting its potential to achieve CCR and prolong PFS.

Keywords: Small cell neuroendocrine carcinoma, etoposide and cisplatin, complete clinical response.

I. INTRODUCTION

Esophageal cancer (EC) is one of the most common and aggressive malignancies worldwide. According to GLOBOCAN 2022, esophageal cancer ranks 11th in incidence and 7th in cancer-related mortality globally.[1] Among these, esophageal squamous cell carcinoma accounts for approximately 85% of all cases and is the most studied subtype.[2]

SCNEC is an extremely rare subtype, accounting for only 0.4% of esophageal cancers and, according to Krishnatreya et al. (2014), is associated with a poor prognosis, with a median overall survival (OS) of approximately 15 months.[3] Management of SCNEC requires a multimodal approach, including chemotherapy, surgery, and radiotherapy. However, treatment outcomes remain limited, and there is currently no standardized treatment regimen for this histological subtype.[4] In Vietnam, there are currently no specific report on the treatment of patients with SCNEC. Therefore, we present this clinical case report to provide additional experience for clinicians in therapeutic practice.

II. CASE REPORT

The patient was a 61-year-old man with no significant past medical history, who presented to Giao Thong Van Tai Hospital with a three-month history of progressive dysphagia.

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Upper gastrointestinal endoscopy revealed an ulcerative, exophytic lesion measuring approximately 1.5 x 2 cm located in the middle third of the esophagus. A biopsy of the esophageal lesion was performed, and immunohistochemical staining showed CK (+), Synap (+), Chromo (+), Ki-67 (+) 80%, CD56 (+), CK5/6 (-), P40 (-) (Figure 2). The results supported the diagnosis of small cell neuroendocrine carcinoma of the esophagus. The patient was subsequently referred to Hanoi Medical University Hospital for further evaluation and management. At the time of diagnosis, the patient's serum NSE level was 24.4 ng/mL. A chest computed tomography (CT) scan performed on January 13, 2024, revealed irregular thickening of the middle third of the esophagus over a 47 mm length, with a maximal wall thickness of 12 mm (Figure 1). The lesion showed indistinct margins with the trachea and carina. A left paratracheal lymph node measuring 34 x 25.3 mm was noted, and neck ultrasonography demonstrated several enlarged left supraclavicular lymph nodes, the largest measuring size of 13 x 10 mm, with loss of normal hilar architecture. Abdominal CT and brain magnetic resonance imaging (MRI) showed no evidence of distant metastasis. Based on these findings, the diagnosis at that time was middle-third esophageal cancer, stage cT4bN2M0, according to the American Joint Committee on Cancer (AJCC) 2017 staging system[5].

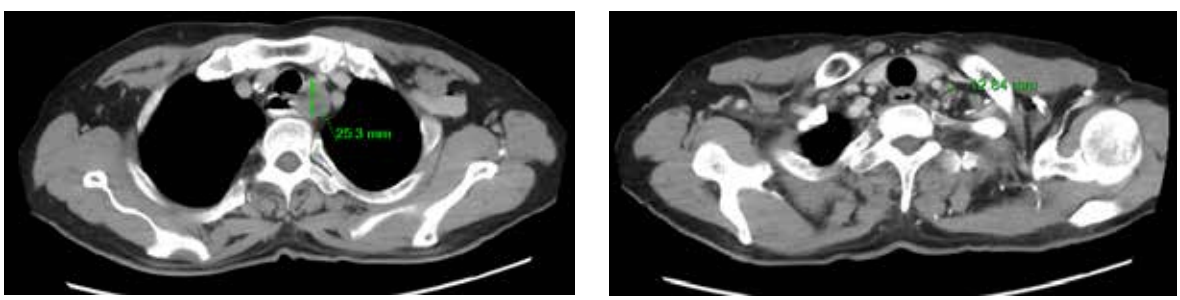

Figure 1. Chest computed tomography (CT) scan at the time of diagnosis on January 13, 2024

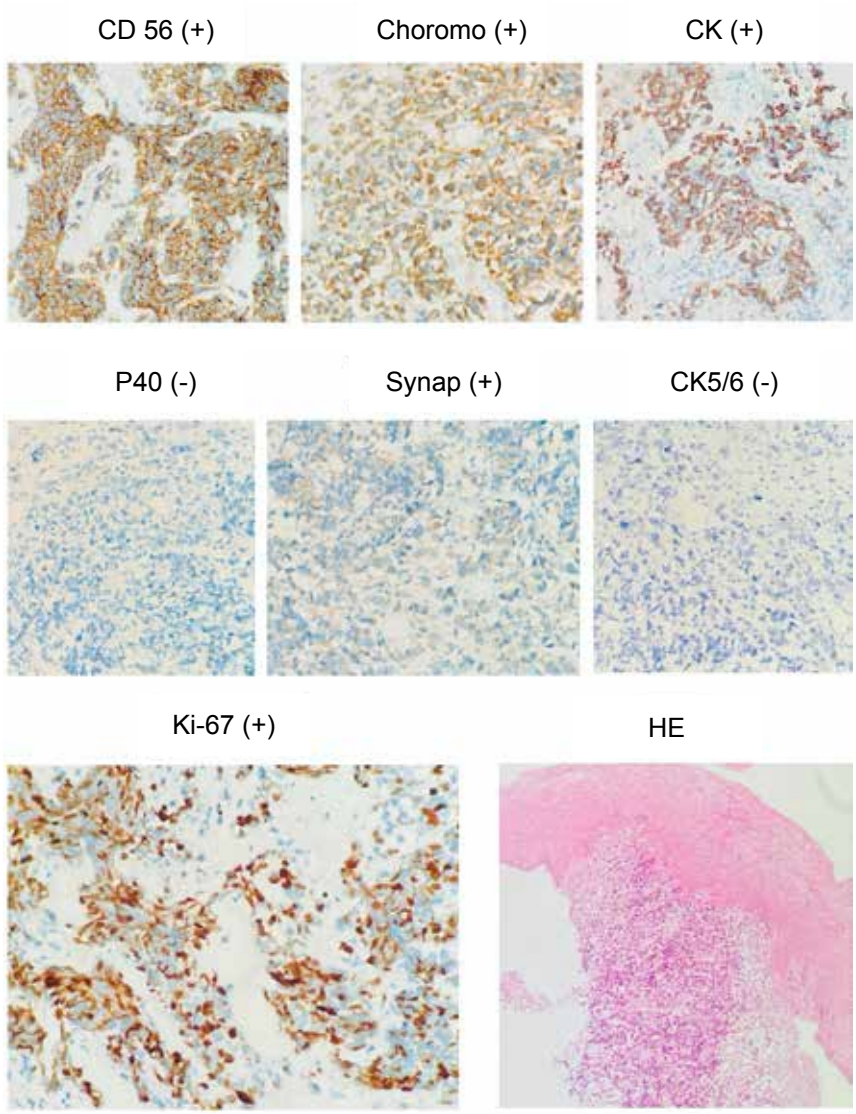

Figure 2. Images of immunohistochemical staining and hematoxylin-eosin (HE) staining

The patient received combination chemotherapy with etoposide and cisplatin (EP) administered over three consecutive days every three weeks, starting on January 15, 2024. After two cycles, re-evaluation on February 26, 2024, showed a decrease in serum NSE level to 15.01 ng/mL. A follow-up chest CT scan demonstrated irregular wall thickening of the middle third of the esophagus over a 42 mm segment, with a maximal thickness of 6 mm and significant reduction in size compared with previous scan (Figure 3). The findings were consistent with a partial response according to RECIST criteria (Version 1.1)[6]. A left paratracheal lymph node measuring 9 x 10.9 mm was still present, but no new lesion was identified. Upper gastrointestinal endoscopy revealed a shallow ulcer located 24-26 cm from the upper incisors, with surrounding mucosal edema. No additional lesion was detected in the pharynx or stomach.

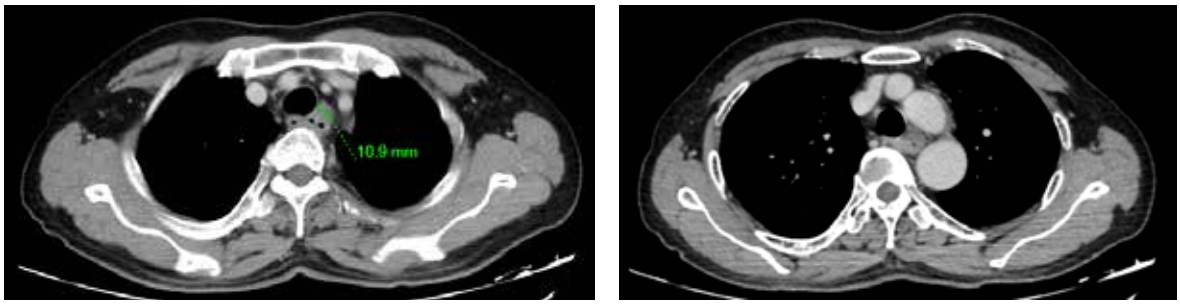

Figure 3. CT scan after two cycles of EP chemotherapy

The patient subsequently underwent concurrent chemoradiotherapy with a total radiation dose of 50.4 Gy in 28 fractions, delivered using intensity modulated radiation therapy (IMRT) in combination with the EP chemotherapy regimen. 99.74% of the planning target volume (PTV) received the prescribed dose of 50.4 Gy, with lung (V20) of 24.25%, and heart (V30) of 20.12%. Radiotherapy was administered from March 6, 2024, to April 24, 2024. During treatment, the patient developed only mild erythema of the anterior chest wall skin, maintained adequate oral intake, and completed the course without any treatment interruptions.

Figure 4. Isodose curves in radiotherapy treatment planning

One month after completion of radiotherapy, follow-up chest CT still showed residual wall thickening in the middle third of the esophagus. Repeat upper endoscopy revealed only a healed scar located approximately 25 cm from the upper incisors, and ultrasonography of the neck demonstrated a left cervical lymph node reduced in size to 7 mm. At that time, the patient's serum NSE level was 11.02 ng/mL, the patient had complete resolution of dysphagia, maintained good oral intake, and remained in stable general condition. The patient then received two additional cycles of EP chemotherapy, starting on May 24, 2024, administered every three weeks. During treatment, on June 12, 2024, he developed grade 4 neutropenia (Neutrophil count of 0.3 G/L) without fever, which was successfully managed with granulocyte colony-stimulating factor (G-CSF) and supportive care. Subsequent blood tests showed full hematologic recovery, and both chemotherapy cycles were completed with good tolerance and no significant non-hematologic toxicity.

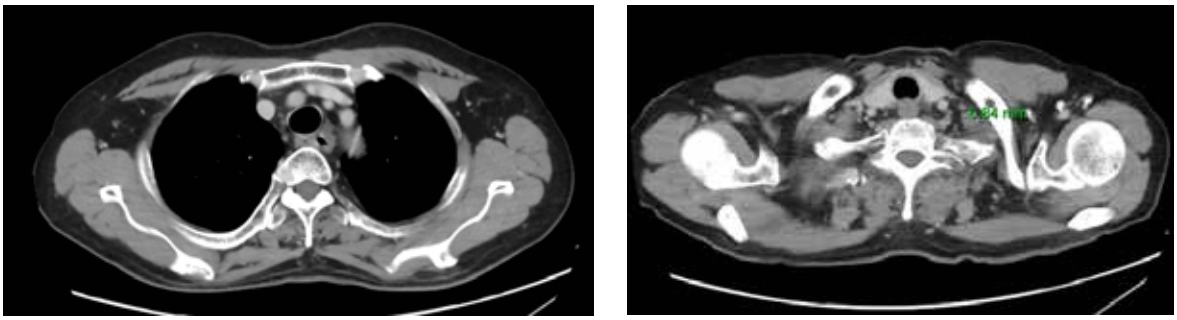

Figure 5. CT scan 1 month after concurrent chemoradiotherapy

At the post-treatment evaluation, the patient's serum NSE level had normalized to 11.15 ng/mL. Follow-up chest CT showed only mild residual wall thickening of the esophagus with a few small adjacent lymph nodes, and ultrasonography of the left cervical region revealed liquefaction of the previously enlarged lymph node. The patient has been followed up every three months, with no evidence of disease recurrence to date.

III. DISCUSSION

In this report, we describe a 61-year-old man who presented with grade 1 dysphagia. Diagnostic evaluation confirmed a middle-third SCNEC, classified as stage cT4bN2M0. At initial presentation, the patient received induction chemotherapy with EP. After two cycles, the tumor size decreased markedly, with esophageal wall thickness reduced from 12 mm to 6 mm, and the left paratracheal mediastinal lymph node decreased from 34 mm to 9 mm. Dysphagia completely resolved, and the patient was able to eat normally. Subsequently, the patient underwent definitive chemoradiotherapy with a total radiation dose of 50.4 Gy in 28 fractions, combined with EP chemotherapy. The tumor continued to regress, leaving only post-radiation ulcerative scar tissue. The tumor marker level normalized, decreasing from 24.4 ng/mL at diagnosis to 11.02 ng/mL. No significant adverse event occurred during radiotherapy. The patient then received two additional cycles of adjuvant EP chemotherapy. After the first cycle, grade 4 neutropenia developed (ANC 0.3 G/L), which was managed successfully with medical treatment. Upon completion of two cycles, the tumor marker level remained stable at 11.15 ng/mL, and chest CT showed only mild residual esophageal wall thickening, achieved CCR. Overall, throughout the entire treatment course, both tumor size and tumor marker levels demonstrated a consistent decrease. Combined chemoradiotherapy with the EP regimen achieved an excellent response, with no evidence of recurrence to date and a PFS of 24 months - substantially longer than that reported in several international studies.[3,7] The main adverse event was chemotherapy-induced neutropenia, which was effectively managed. No other significant complication was observed.

Small cell neuroendocrine carcinoma (SCNC) is most commonly identified in lung cancer, accounting for approximately 13% of all lung cancer cases, this malignancy is rarely reported in other organs, such as the larynx, pancreas, stomach, prostate, uterus, gallbladder, and esophagus.[4,9] SCNEC is a rare and highly aggressive histological subtype, first described by McKeown in 1952.[3] According to a study by Manigreeva Krishnatreya et al. (2014), among 2,487 patients with esophageal cancer, only 11 cases (0.4%) were identified as SCNEC.

The reported median OS was 15 months, with a 22-month survival rate of 36%.[3]

SCNEC occurs more frequently in males than in females, with a reported male-to-female ratio of approximately 3/2, the mean age at diagnosis is 72 years old, which is older than that observed in the clinical case presented in our report. Tumors are most commonly located in the lower third of the esophagus, followed by the middle third. Identified risk factors include cigarette smoking, advanced age, alcohol consumption, and a high-salt diet. Clinical manifestations are generally nonspecific and include dysphagia, odynophagia, weight loss, dyspepsia, and anorexia. The average interval from symptom onset to diagnosis is approximately 4 months. Diagnosis is established by endoscopic biopsy, and staging is performed using CT and PET/CT.[10]

Histopathologically, on light microscopy with HE staining, the tumor is characterized by the presence of small cells with round to spindle-shaped morphology, arranged in a diffuse pattern or in nests. These cells typically exhibit scant cytoplasm, inconspicuous or absent nucleoli, and finely granular chromatin. On immunohistochemical analysis, SCNC commonly demonstrates positivity for neuroendocrine markers such as synaptophysin (Syn), chromogranin A (CgA), along with cytokeratin (CK) and CD56. The Ki-67 proliferation index is usually high, exceeding 50% in most cases. In our clinical case, the tumor showed positivity for all of the aforementioned markers, with a Ki-67 index of 80%. Notably, immunohistochemical markers have prognostic as well as diagnostic significance. Patients with CgA-positive tumors have been reported to have longer overall survival compared with those with CgA-negative tumors. Furthermore, patients whose tumors express at least one of the following markers, including thyroid transcription factor-1 (TTF-1), NSE, Syn, or CgA, demonstrated a more favorable prognosis than those negative for all these markers, with a mean overall survival of 15.3 months versus 6.1 months, respectively (P = 0.002).[9,10]

SCNEC is commonly staged using the AJCC TNM system and the Veterans Administration Lung Study Group (VALSG) classification, which categorizes disease into limited-stage (LS) and extensive-stage (ES). Limited-stage disease is defined as a tumor confined to the esophagus and/or adjacent tissues, with or without regional lymph node metastasis, whereas ES includes distant metastases.[11] More than half of patients with esophageal small-cell carcinoma present with metastatic disease at the time of diagnosis, underscoring the critical importance of accurate staging in guiding optimal treatment strategies.[11,12]

The prognosis of SCNEC depends on several factors, including disease stage, patient age, tumor size, and treatment modality. This was demonstrated in a study by Casas et al (1997) involving 199 patients with esophageal SCNEC, which showed a statistically significant difference in overall survival between patients with LS and ES disease, with median OS of 8 months and 3 months, respectively ($p < 0.0001$).[13] Univariate analysis identified several important prognostic factors, including age, tumor size, and treatment approach. Patients aged ≤ 60 years old had an OS of 11 months, compared with 6 months for those aged > 60 years old. Tumor size also significantly influenced survival, with a median OS of 12 months for tumors ≤ 5 cm and 4 months for tumors > 5 cm. Furthermore, patients who received combined systemic and local therapy had a markedly longer median OS of 20 months, compared with 5 months in those treated with local therapy alone.[13] In multivariate analysis,

tumor size (p = 0.007) and treatment modality (p < 0.001) were identified as independent prognostic factors significantly associated with OS.[13]

Based on these findings, the efficacy of combined systemic and local treatment approaches has continued to be reported in patients with SCNEC. In a retrospective study by Chikatoshi Katada et al. (2020) involving seven patients treated with EP chemotherapy combined with definitive radiotherapy (50.4 Gy in 28 fractions), the median OS was 32 months, and the complete response rate was 100% (7/7). Among these, 43% (3/7) of patients experienced disease recurrence, while the median OS for the four non-recurrent patients was 56 months.[8] In addition, grade 3 or 4 toxicities were reported, including neutropenia (100%), thrombocytopenia (43%), febrile neutropenia (43%), and nausea (14%). Although the incidence of hematologic toxicity was relatively high, all seven patients were able to complete the planned treatment. The authors concluded that definitive radiotherapy combined with EP chemotherapy is a feasible therapeutic approach that can prolong survival in selected patients.[8] Therefore, the EP regimen combined with radiotherapy at 50.4Gy/28 fractions was selected as the preferred treatment approach for the patient in our report.

Surgical resection is also considered a potentially curative treatment option for esophageal small cell neuroendocrine carcinoma. However, it is a highly invasive procedure associated with a significant risk of postoperative complications and mortality. In a large analysis of 11,943 patients who underwent esophagectomy, 63.9% experienced postoperative complications, and 3.3% died from severe adverse events such as anastomotic leakage, respiratory failure, renal failure, or reintubation requirement.[14] Moreover, the benefit of surgical intervention in esophageal small cell neuroendocrine carcinoma remains uncertain and is generally reserved for patients with early-stage disease without lymph node metastasis. In a study by Usami et al (2010) involving 47 patients, the authors concluded that surgery provided a long-term survival benefit only in patients without lymph node involvement.[15] At the initial evaluation, the patient in our report was staged as cT4bN2M0, with metastatic lymph node involvement identified on chest CT. Therefore, concurrent chemoradiotherapy was prioritized over curative surgery as the preferred treatment approach.

Our report shows that concurrent chemoradiotherapy in a patient with localized SCNEC achieved a favorable outcome, with CCR after treatment and a PFS of 24 months to date. However, the limitation lies in the single-case nature of the report, which does not allow generalization to other cases of esophageal SCNEC. Therefore, larger studies are needed to strengthen treatment strategies and provide more specific clinical guidance for this histologic subtype.

IV. CONCLUSION

Small cell neuroendocrine carcinoma of the esophagus is a rare histopathological subtype, and no standardized treatment guideline has yet been established. In our case, combined therapy with EP chemotherapy and radiotherapy achieved durable disease control, with no recurrence observed nearly two years after treatment. This report may serve as a basis for future studies aimed at defining optimal management strategies for this uncommon malignancy.

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