

Apatinib combined with concurrent chemoradiotherapy in patients with subglottic small cell carcinoma: a case report

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Abstract

Subglottic small cell carcinoma (SSMCC) is a rare type of neoplasm, meaning that laryngeal cancer guidelines in several countries, including the National Comprehensive Cancer Network (NCCN) guidelines, do not include treatment principles for SSMCC. Angiogenesis is an established factor in tumor initiation, growth, and dissemination. Apatinib mesylate, an orally administered drug, is a novel inhibitor of vascular endothelial growth factor receptor-2, a key mediator of angiogenesis, and has been shown to be safe and efficacious in the treatment of certain types of malignant tumors. To the best of our knowledge, there are few reports on the treatment of SSMCC with apatinib combined with concurrent chemoradiotherapy. In the present report of SSMCC in a 64-year-old woman, oral apatinib was given daily at a dose of 250 mg in combination with concurrent chemoradiotherapy; the only toxicities reported were mild leukopenia and finger numbness. Clear and rapid efficacy was observed with the disappearance of the tumor mass. Our findings indicate that apatinib combined with concurrent chemoradiotherapy may be effective in patients with SSMCC, with adverse reactions within the manageable range, thus representing an additional treatment option for this type of malignancy.

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Keywords

Apatinib, subglottic small cell carcinoma, concurrent chemoradiotherapy, angiogenesis, vascular endothelial growth factor receptor-2 inhibitor, laryngeal cancer

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Introduction

Although small cell carcinoma (SMCC) is most commonly found in the lung, extrapulmonary small cell carcinoma (ESMCC) accounts for about 2% to 4% of all SMCC cases.¹ SMCC is rarely diagnosed in head and neck tumors, which comprise 10% to 15% of all ESMCCs.² Laryngeal small cell carcinoma (LSMCC) is a rare type of neuroendocrine carcinoma, representing fewer than 0.5% of all laryngeal cancers.³ Among all laryngeal malignancies, approximately 5% are subglottic carcinomas.^{4–8} Subglottic SMCC (SSMCC) is thus an even rarer form of SMCC. The first case of LSMCC was described by Olofsson and Van Nostrand in 1972⁹ and the second by Ferlito in 1974.^{10,11} ESMCC presents similar clinicopathologic features to small cell lung carcinoma (SCLC).^{2,12} In the past 30 years, 160 cases of LSMCC have been reported, mostly occurring in the head and neck region.^{13,14} Up to 2015, approximately 200 cases of LSMCC have been reported globally.¹⁵ Therefore, SSMCC is quite rare.

Early-stage SSMCC is largely asymptomatic, but the disease is highly malignant with locally aggressive tumors and a poor prognosis. However, the low incidence of SSMCC means that not many clinical cases have been reported, leading to uncertainty over the optimal treatment strategy. Several studies have shown that early subglottic cancer can be treated with monotherapy, while advanced disease requires radiotherapy in combination with

chemotherapy.^{5–7,16–19} However, a study by Lin et al.²⁰ failed to demonstrate that combination therapy provided significant survival benefits over monotherapy. Apatinib, a small-molecule agent targeting vascular endothelial growth factor receptor-2 (VEGFR-2), has been shown to control occurrence and development of tumor tissue.^{21,24–28} Evidence regarding apatinib and concurrent chemoradiotherapy in SSMCC has not been reported previously, although some studies have reported promising efficacy and safety of apatinib in SCLC.^{22,23} Therefore, in our patient with SSMCC described in the present case, we selected apatinib as a targeted therapy in combination with radiotherapy and chemotherapy.

Presentation of the case

Our patient was a 64-year-old woman with a history of progressive throat pain and worsening hoarseness. Five months after the onset of symptoms, the patient complained of progressive dyspnea and increasing difficulty in swallowing regular food. There was no history of any malignancy in the patient's family. In September 2019, she attended the First Affiliated Hospital of Bengbu Medical University where direct laryngoscopy revealed new growth below the subglottic region of the larynx (Figure 1a and 1b). No distant metastases were identified on radiology tests, and the patient underwent a biopsy of the lesion. Histopathological examination showed

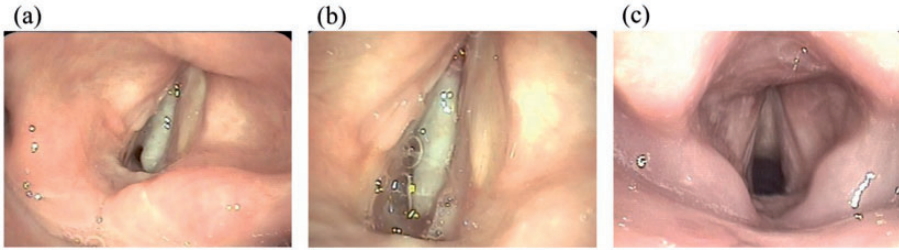


Figure 1. Laryngoscopic results: before treatment (September 2019): (a), (b) New growth can be seen under the glottis, with poor glottal movement on both sides. After treatment (August 2020): (c) A bulge is visible under the glottis, the surface is smooth, and bilateral movement is normal.

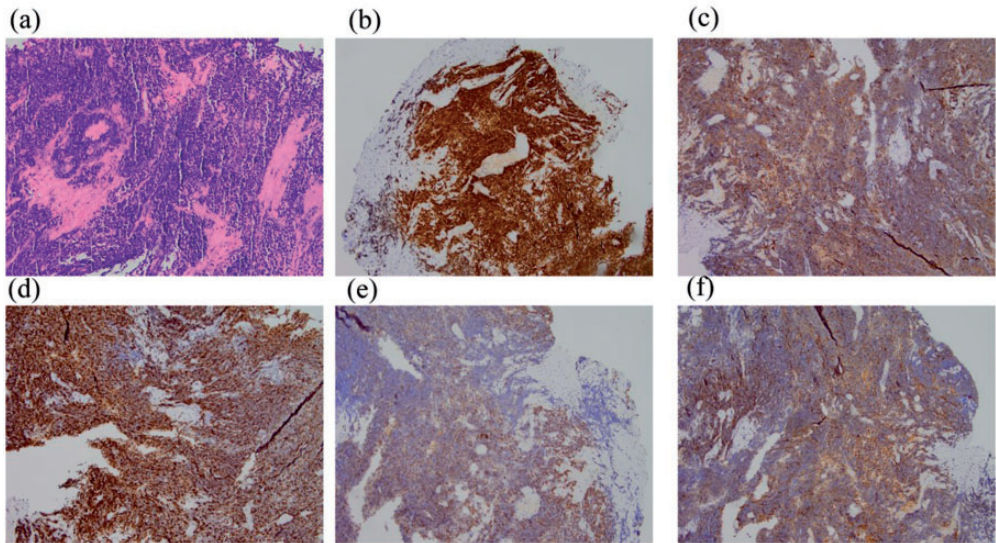


Figure 2. Pathological results: (a) hematoxylin and eosin staining revealing small, round cells with scarce cytoplasm and deeply stained nuclei, suggesting a round cell tumor (original magnification, 100 \times). Immunohistochemical results (b–f): (b) TTF-1 (+); (c) Syn (+); (d) KI-67 (+, 80%); (e) CK (+); (f) CD56 (2+).

small round cells with sparse cytoplasm and deep nuclear staining, suggesting a round cell tumor (Figure 2). Immunohistochemistry results included TTF-1 (+); Syn (+); KI-67 (+, 80%); CK (+); and CD56 (2+) (Figure 2). Postoperative pathology (pathology no.: IHC20194228) indicated SSMCC. The patient underwent a tracheotomy to relieve her breathing. Magnetic resonance imaging (MRI) was also performed (Figure 3a–c).

The patient started radiotherapy at a dose of 70 Gy in 33 fractions in December 2019, with weekly cisplatin (50 mg) administration to improve local control. In addition, the patient received apatinib (250 mg/day) as a targeted therapy. During treatment, the general condition of the patient improved considerably. Computed tomography (CT) imaging revealed a clear reduction in the laryngeal focus, and laryngeal lesions indicated complete remission (CR)

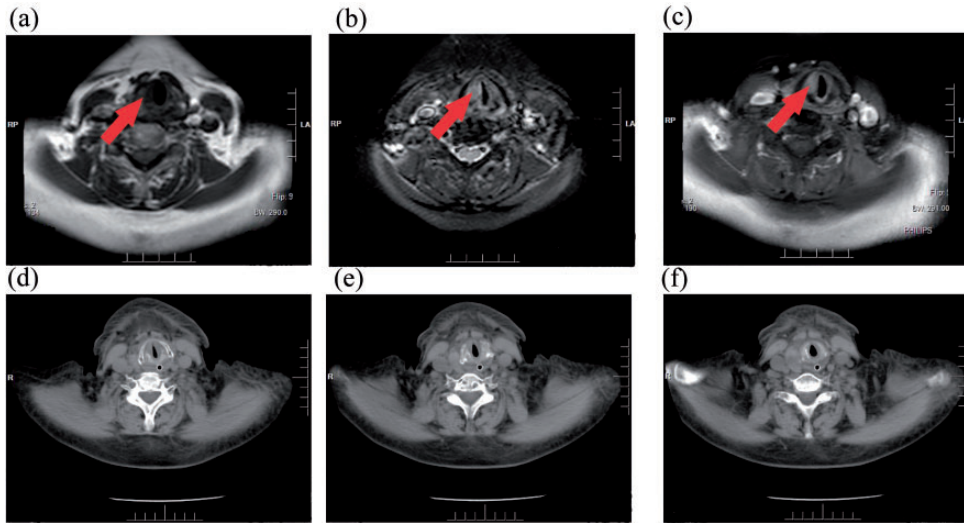


Figure 3. (a–c) MRI showed that the soft tissue shadow of the right side of the vocal cord mucosa of the larynx was significantly thickened. (d–f) CT imaging showed that the right-side sound band was slightly thickened, with reduced soft tissue shadow thickness.

on clinical evaluation. The results of laryngoscopy after treatment are shown in Figure 1c.

Discussion

Primary subglottic carcinoma, a rare neoplasm, accounts for fewer than 5% of all laryngeal malignancies. Squamous cell carcinoma is the most common histologic type, accounting for 55% to 66% of all tumors.^{5,29,30} The sublaryngeal glottis is located 5 mm below the free edge of the vocal cords and extends into the submucosa of the annular cartilage,³¹ including lateral cartilage and inner pineal gland.³² Some studies suggest that smoking and excessive alcohol consumption are the main risk factors for the occurrence and development of laryngeal cancer.^{33,34} Furthermore, a relationship between *Helicobacter pylori* infection and pharyngeal cancer has been reported, but remains controversial.^{35–38} LSMCC predominantly affects men in the 50-to-70-year age group,^{1,39} particularly those with a history of heavy smoking.¹³

The clinical symptoms of LSMCC are similar to those observed in patients with laryngeal cancer, including hoarseness, difficulty in breathing and/or swallowing, coughing, blood in sputum, and neck lumps, although the first three manifestations are the most common.^{14,40} Primary SMCC of the head and neck region has a poor prognosis, being a rapidly progressive and highly invasive malignant tumor with a tendency to increased metastasis and invasion; cautious examination with a thorough systemic evaluation for metastasis is thus warranted in these patient.¹³ The 3- and 5-year survival rates for SMCC are 30% and 11% to 13%, respectively.³³ The World Health Organization has classified SMCC and poorly differentiated (grade III) neuroendocrine tumors as belonging to the same pathological type.⁴¹ Given the rarity of this tumor type, laryngeal cancer guidelines, including National Comprehensive Cancer Network (NCCN) guidelines, do not provide a treatment strategy for this malignancy in many countries.⁴² Therefore, the

optimal treatment for SSMCC remains unclear. Treatment selection in our patient was primarily derived from the treatment of SCLC and other reported SSMCC cases. Several recent studies have confirmed that radiotherapy can preserve laryngeal function in patients with glottic cancer,^{6,17,43} while no reduction in mortality has been observed among patients with locally advanced laryngeal cancer treated with surgery in combination with radiotherapy and chemotherapy.⁴⁴ In addition, Pointer et al.¹ emphasized that chemotherapy combined with radiation therapy might be beneficial in patients with LSMCC at the least toxic and most effective therapeutic regimen. Therefore, we treated our patient simultaneously with combined chemoradiotherapy. Four months later, brain CT revealed no metastases and we the patient continues in follow up.

Angiogenesis is a key factor in tumor initiation, growth, and dissemination.⁴⁵ Apatinib, a small molecule tyrosine kinase inhibitor (TKI), inhibits endothelial cell migration and proliferation, thus preventing tumor neovascularization.⁴⁶ In recent years, antiangiogenic drugs have been widely used in the treatment of malignant tumors but have been associated with adverse reactions such as gastrointestinal disturbances, hypertension, and myelosuppression.⁴⁷ In the present case, we selected apatinib over other TKIs because of the patient's financial situation. To our knowledge, there are few reports of LSMCC treatment using apatinib combined with concurrent radiotherapy and chemotherapy. During treatment, the patient reported only mild leukopenia and finger numbness, while other known adverse drug reactions such as hypertension and albuminuria were not observed. This successful case provides new evidence for the use of antiangiogenic drugs in the treatment of patients with less-prevalent malignant tumors. CT imaging (Figure 3d–f) showed a dramatic reduction

in the tumor compared with pre-treatment MRI imaging (Figure 3a–c). In the present case, the addition of antiangiogenic drugs significantly improved the outcome of our patient, who achieved a CR with no significant association between apatinib treatment and the side effects associated with radiotherapy and chemotherapy. On monthly review, laryngoscopy showed no recurrence after 11 months. This points to a synergistic effect of apatinib combined with concurrent chemoradiotherapy, although the underlying mechanism of their interaction requires further investigation. In addition to angiogenesis inhibition, the anti-tumor effect of apatinib has recently been shown to involve multiple pathways in specific malignancies,^{48–51} although its application in LSMCC has not been widely reported. To our knowledge, few reports have described the treatment of SSMCC with apatinib combined with radiotherapy and chemotherapy. Although the present report of a single case describes a successful outcome, prospective trials in large numbers of patients are needed to ascertain the underlying role of apatinib combined with radiotherapy and chemotherapy in LSMCC.

Conclusion

Apatinib combined with concurrent chemoradiotherapy may represent a potential treatment for patients with LSMCC. This case report provides evidence for a new treatment strategy for this rare tumor type.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Ethics statement


The reporting of this study conforms to CARE guidelines. We have de-identified the details such that the identity of the patient may not be ascertained in any way. Written informed consent was

obtained from the patient for the biopsy, treatment, and case publication. Ethics committee/institutional review board approval was not sought due to the nature of the study (case report).

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