Photodynamic therapy with local-targeted perfusion for recurrent tracheal adenoid cystic carcinoma achieving 12-year survival: A case report

LUOQI YANG, LU WANG, HONGWU WANG and HENG ZOU

Respiratory Disease Center, Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, Beijing 100700, P.R. China

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Abstract. Adenoid cystic carcinoma (ACC) is a malignant tumor that originates from the ductal epithelium of the secretory glands and has a tendency for perineural invasion. Primary tracheal ACC is a clinically rare subtype, with an annual incidence rate of 0.04-0.2%, accounting for <1% of all tracheal malignant tumors. Surgery and radiotherapy remain the standard treatments, but there are clinical challenges with the high recurrence rate. The present article reports the case of a patient who relapsed after partial tracheal resection and was considered inoperable. Bronchoscopy was used for airway assessment and interventional treatment, including submucosal injection and photodynamic therapy. After this intervention, the overall survival of the patient exceeded 12 years.

Introduction

Adenoid cystic carcinoma (ACC) is a malignant basal cell-like tumor originating from the ducts of secretory glands, the pathological features of which are the biphasic differentiation of glandular epithelium and myoepithelial cells. The incidence of ACC accounts for ~1% of malignant tumors in the head and neck region (1-3). Notably, ACC is more common in people aged 40-60 years and there is no notable difference in sex distribution (4). Although disease progression for ACC is relatively slow and the histological grade is often low, ACC has a high tendency of neural invasion and long-term recurrence, thus resulting in a 10-year survival rate of ~40% (5).

At present, surgical resection remains the first-line treatment option for ACC, but it faces three major clinical challenges (6): i) Due to the infiltration and growth of the tumor along the perineural area, it often leads to a high positive rate of the surgical margin; ii) the local recurrence rate after surgery is >50%, and it is often accompanied by symptoms related to nerve invasion; and iii) ACC is poorly responsive to conventional radiotherapy and chemotherapy, as evidenced by an objective response rate of <20%. The present study describes the case of a patient with ACC in the middle and upper trachea who experienced recurrence 2 months after undergoing standard partial tracheal resection. The adoption of a comprehensive intervention strategy combining photodynamic therapy (PDT) with local targeted drug perfusion may provide a novel treatment option with notable survival benefits for patients with advanced ACC who are no longer eligible for surgery.

Case report

The patient was a 45-year-old woman who first experienced intermittent dyspnea in November 2013, which worsened after physical activity. The patient initially sought care at a secondary general hospital in Beijing, China, where they were diagnosed with and treated for bronchial asthma. The received pharmacotherapy included standard bronchodilators, such as β2-adrenergic agonists and theophylline. After 6 months of treatment, the symptoms exhibited by the patient did not display notable improvement. Subsequently, the patient was referred to a tertiary hospital (Beijing, China) for further investigation. In April 2014, a chest CT scan performed at the tertiary hospital showed diffuse circumferential thickening of the airway walls, with infiltrative growth along the long axis of the trachea and a space-occupying lesion detected in the upper segment of the trachea (Fig. 1A). Bronchoscopy revealed a large, broad-based mass in area II, blocking 90% of the lumen (Fig. 2A). Physical examination exhibited coarse breath sounds in both lungs, with audible dry and wet rales, and wheezing in the anterior chest area. The functional status of the patient was assessed as follows: Modified Medical Research Council (mMRC) (7) dyspnea grade, 3; quality of life (QOL) score (8), 30/60; Karnofsky Performance Status (KPS) (9), 60. Bronchial artery embolization and electroresection of the endotracheal tumor were performed later in April 2014, and the postoperative histopathology reported tracheal ACC (TACC).

In July 2014, the patient underwent partial tracheal resection and artificial airway implantation at an external tertiary

Correspondence to: Professor Hongwu Wang or Dr Heng Zou, Respiratory Disease Center, Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, 5 Haiyun Cang, Dongcheng, Beijing 100700, P.R. China
E-mail: wanghongwu2015@126.com
E-mail: zouhang75@126.com

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hospital (Beijing, China). The specimens of the resected trachea showed that the entire trachea was involved, the entire layer of the trachea wall was invaded, nerve invasion was visible, and tumor components could be seen at both resection margins. After discharge, the patient was admitted to Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine (Beijing, China) for subsequent management. After 2 months, the patient experienced recurrent shortness of breath after activity, accompanied by wheezing. Bronchoscopy revealed circumferential stenosis at the lower anastomosis of the artificial trachea. Electrocautery and dilation attempts failed to resolve this obstruction. In January 2015, an hourglass-shaped tracheal silicone stent (diameter 14-12-14 mm; length 15-20-15 mm) was placed in areas I-II (Figs. 1B and C, and 2B and C). The patient reported that the symptoms had improved following treatment.

Over the following 7 years, the patient's condition remained stable. In March 2022, due to progressive dyspnea, a bronchoscopy was performed, revealing a new growth at the lower edge of the stent. Pathological examination suggested ACC, which was considered a recurrence (Fig. 2C). After comprehensive consideration, the patient received three sessions of PDT using HiPorfin (a hematoporphyrin derivative), which was administered intravenously at 2 mg/kg. Light activation was performed 48 h post-infusion using a 630-nm semiconductor laser delivered through 3-cm cylindrical-diffuser fibers at 100 mW/cm^2 (total energy, 1,428 J over 1,380 sec), achieving a fluence of 168 J/cm^2 per treatment. Procedures were conducted under dual-channel bronchoscopic guidance (Fig. 2D). In April 2022, a bronchoscopy and biopsy showed no tumor cells (Fig. 2E). In May 2022, the lesion area was notably reduced compared with before (Fig. 2F). From June to November 2023, the patient received eight cycles of bronchoscopy-guided submucosal-injection therapy. Each treatment session utilized a combination of Endostar® (15 mg, 3 ml) and cisplatin (10 mg, 3 ml), administered via a disposable endoscopic injection needle (total length, 120 cm; exposed needle tip, 6 mm; outer diameter, 2.4 mm). During the procedure, the injection needle was fully extended (6 mm) under direct visualization to penetrate the mucosal layer. Quadrant injections were performed at the 3, 6, 9 and 12 o'clock positions around the lesion margins, with 0.5-1 ml of the Endostar and cisplatin solution administered per injection point (total dose, 6 ml per cycle). The functional outcomes were: mMRC dyspnea, 1; KPS, 90; QOL score, 55/60. Quantitative analysis revealed >50% improvement in key functional parameters post-PDT. The patient was maintained under strict monitoring throughout the entire hospitalization and treatment period. The most recent assessment conducted in March 2025 showed a good treatment response; it was observed that the inflammatory reaction at the upper edge of the stent was 0 points, granulation hyperplasia was 0 points and the retention of secretions within the stent was grade 1 under bronchoscopy (10,11). The inflammatory reaction at the lower left edge of the stent was 1 point. A tissue biopsy was obtained via bronchoscopy, and pathological examination diagnosed the inflammatory reaction as mucosal inflammatory granulation tissue (data not shown). The comprehensive 12-year treatment schedule for the patient is shown in Fig. 3.

Discussion

The primary sites of ACC are most commonly the parotid gland, palate and sublingual gland, although it can also occur in the trachea and bronchi, as well as in the breast, cervix and other sites (12). Among these occurrences, primary ACC of the trachea is particularly rare, with an annual incidence rate of only 0.04-0.2% (6). Furthermore, the early symptoms of primary ACC of the trachea lack specificity, and often manifest as progressive dyspnea, cough and expectoration, accompanied by wheezing (13,14). Such manifestations are confused with benign airway diseases (such as asthma or chronic bronchitis), resulting in a delayed diagnosis. The neuroendocrine-driven infiltration and longitudinal spread along the tracheal wall can mimic the appearance of benign inflammatory or infectious processes, often leading to misdiagnosis (15). The present case depicts this typical misdiagnosis. The patient had wheezing and shortness of breath after activity; leading to an initial misdiagnosis of bronchial asthma. Unfortunately, no CT or bronchoscopy was performed, making it impossible to assess airway lesions at the onset of the disease. It was not until the asthma medication proved ineffective that CT showed diffuse ring-shaped thickening of the tracheal wall, accompanied by a space-occupying lesion in the upper segment of ~2.3 cm, thus confirming the diagnosis of ACC.

Due to the characteristics of slow growth, local invasion, distant metastasis, nerve invasion and recurrence of ACC, the tumor range far exceeds the visible and palpable range and the surgical margin is difficult to determine. These factors result in a poor local control rate (14). For salivary gland tumors, in addition to as much resection as possible, total or subtotal resection of the maxilla is also required (16). For large tumors involving the base and movable tongue, traction or mandibular resection is required. If there is extensive nerve infiltration, even if a thorough assessment and expanded resection are conducted before the operation, it is still difficult to ensure that the resection margin of ACC is negative (17). For tumors at stage T3-T4, complete resection is impossible and palliative resection is performed instead (18). The difficulty of palliative resection lies in weighing the functional and aesthetic damage caused by surgical trauma and the negative impact of these factors on patients. Radiotherapy can overcome the surgical constraints associated with the unique anatomical location of the tumor, kill tumor cells that have invaded the surroundings of the tumor or spread along nerves and blood vessels, and treat the areas with lymphatic drainage. High-energy X-rays can activate the p65 signaling pathway in ACC and control the local recurrence rate (19). However, ACC is a malignant tumor with poor sensitivity to radiotherapy and enhancing the radiotherapy dose poses the risk of radioactive damage. A report on ACC of the jaw by Li *et al* (20) proposed that a postoperative radiotherapy dose of ≥60 Gy had no effect on survival rate, whereas a postoperative radiotherapy dose of <60 Gy reduced the survival rate of the patient. A study by Huang *et al* (21) reported that the local tumor control rates of patients with head and neck tumors at 2, 5 and 10 years after brachytherapy were 86.3, 59.0 and 31.5%, respectively. The overall survival rates at 2, 5 and 10 years were 92.1, 65.0 and 34.1% respectively. Despite active surgery and radiotherapy on ACC, multiple local relapses are common, and the long-term

Figure 1. Tracheal adenoid cystic carcinoma. (A) CT scan of tracheal space-occupying lesion. (B and C) CT scan after silicone stent implantation. (B) CT scan showing the upper edge of the silicone stent after implantation. The silicone stent is closely attached to the trachea, and the image displays the condition of the upper part of the stent within the tracheal structure, with the stent fitting well in this region. (C) CT scan depicting the lower edge of the silicone stent post-implantation. The silicone stent is fitted closely to the trachea, and the image presents the condition of the lower part of the stent in relation to the trachea and surrounding lung tissue, indicating the position of the lower section of the stent. CT, computed tomography.

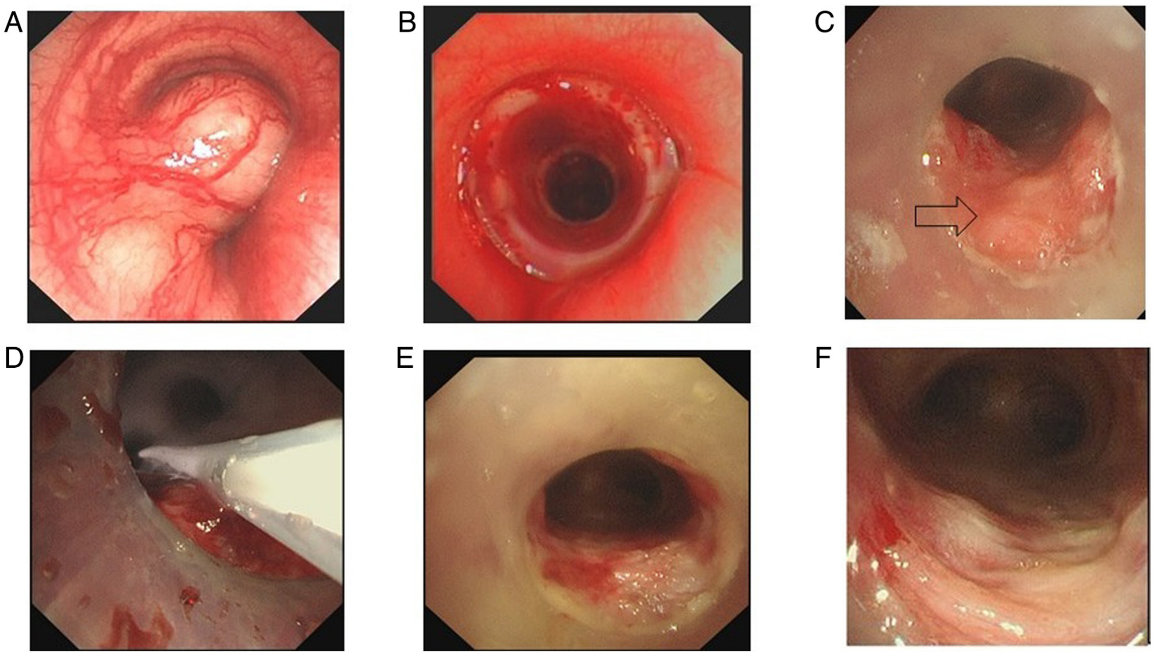

Figure 2. Bronchoscopy examination and interventional treatment. (A) Broad pedicle mass in tracheal area II. (B) Upper edge of the silicone stent. (C) Lower edge of the silicone stent, with the black arrow indicating the site of tumor recurrence. (D) Under bronchoscopy, the bronchoscope and the optical fiber (white columnar object) for PDT were visible, closely attached to the tumor recurrence site. (E) Local mucosal redness and swelling after PDT. (F) Bronchoscopy reexamination 1 month after PDT showed white necrotic material. PDT, photodynamic therapy.

prognosis is poor. The focus of clinical treatment for ACC is to identify effective postoperative adjuvant treatment regimens.

The recurrence of ACC in the patient described in the present case 2 months after surgical resection highlights the treatment dilemmas of TACC: i) The biological characteristics of perineural infiltration, where tumor cells grow invasively along the nerve bundle membrane space, thus making it difficult to evaluate the postoperative resection margin. ii) Irreversible damage to the anatomical structure. Artificial airway reconstruction was performed during the first operation in the present case, and the recurrent lesion was located at the distal end of the stent-tracheal anastomosis. Notably, the second operation may cause airway collapse or anastomotic fistula. iii) Resistance to radiotherapy and chemotherapy. ACC tumors have low sensitivity to traditional radiotherapy and chemotherapy, and traditional systemic treatment is limited. As a result, PDT has become a key alternative due to its dual selectivity mechanism (22).

PDT achieves selective tumor destruction through well-defined biological processes (23,24). Firstly, photosensitizers specifically accumulate in malignant tissues through the high permeability and retention effect of tumor tissues, and the upregulation of low-density lipoprotein receptors on the surface of cancer cells. Their concentration can reach 5-10 times that of normal tissues, and they have no systemic toxicity at therapeutic doses (25). The important stage of action begins with laser activation: When a specific wavelength light source (such as 630 nm red light) activates the photosensitizers, a type II photochemical reaction occurs, converting ground-state oxygen ($^3O_2$) into highly cytotoxic singlet oxygen ($^1O_2$). The reactive oxygen species $^1O_2$ has an extremely short diffusion radius (<0.02 μm), and directly induces the apoptosis and necrosis of cancer cells by oxidizing and damaging lipid membranes, proteins and mitochondrial DNA. It is worth noting that this process precisely targets the diseased cells, and the basement membrane structure is completely preserved

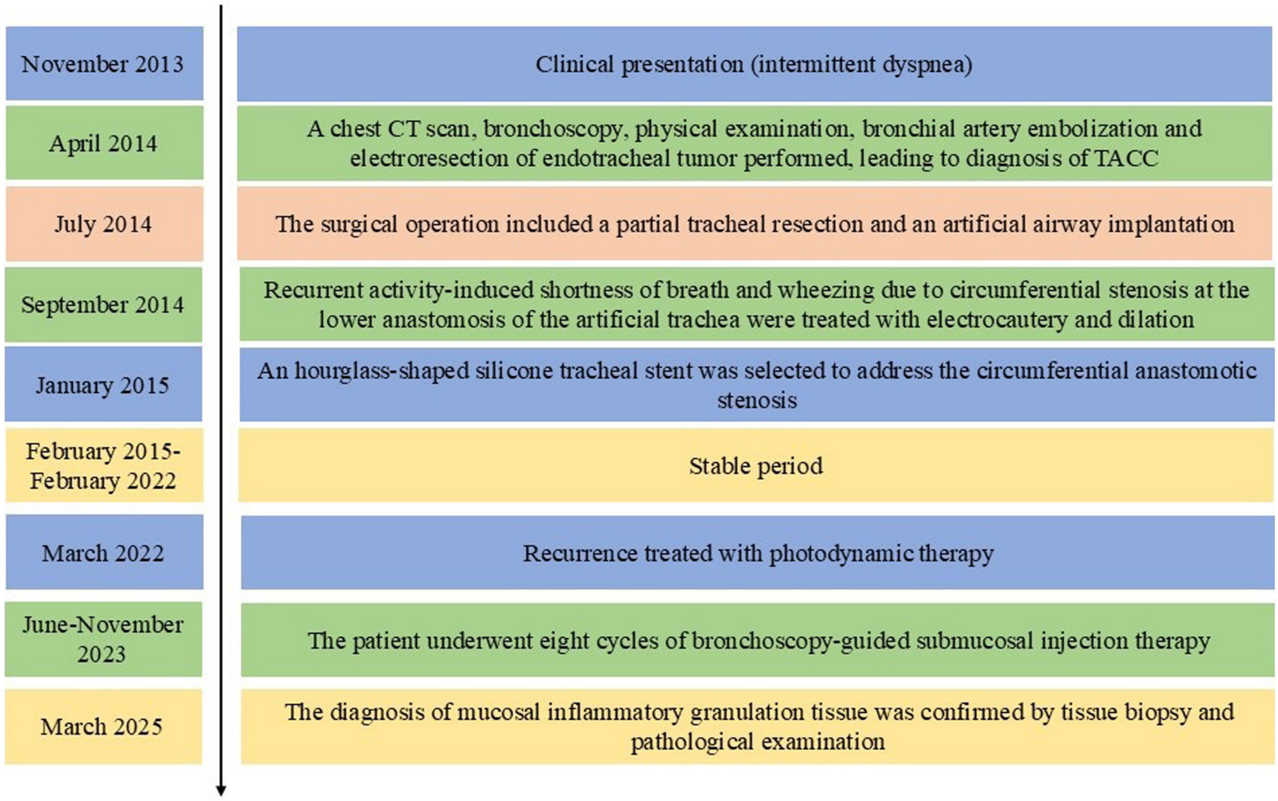

Figure 3. Comprehensive patient treatment timeline. TACC, tracheal adenoic cystic carcinoma.

due to the strong resistance of collagen components to oxidative damage, which is important for maintaining the stability of the airway structure (25,26). In addition, the efficacy of PDT stems from the multimodal antitumor mechanism: $^1O_2$ causes vascular endothelial damage, leading to platelet aggregation and microthrombosis. These outcomes not only inhibit tumor blood supply and hinder regeneration, but also markedly reduce the risk of bleeding from the lesion. When tumor cells die, they release damage-associated molecular patterns, such as calreticulin and HMGB1, to recruit dendritic cells and enhance cytotoxic T-lymphocyte responses, generating systemic antitumor immunity (27). Particularly in cases of central lung cancer, the systemic antitumor immune response can notably preserve the normal ventilation function of the lungs (28,29). The combined application of PDT with submucosal injection forms a synergistic effect. Local injection of Endostar can increase the permeability of tumor cell membranes and promote the intracellular enrichment of cisplatin. Subsequently, enriched cisplatin effectively inhibits micrometastasis by binding to DNA and interfering with its replication, and Endostar blocks the vascular endothelial growth factor pathway to prevent angiogenesis. The plasma concentration of cisplatin after mucosal injection is only 1/10 of the dose during intravenous administration, avoiding systemic toxicity such as bone marrow suppression (30). This minimally invasive sequential treatment mode achieves a dual reduction in tumor burden, notably improves airway function and continuously benefits the QOL of patients.

The present case supported the concept that for inoperable advanced central ACC, PDT combined with mucosal targeted injection of cisplatin and Endostar can not only prolong progression-free survival, but also markedly improve the QOL by enhancing airway function. It is worth noting that PDT has limited control over deep tumor invasion and needs to be combined with local drug injection to remove residual lesions. The present case emphasizes that PDT may be regarded as a palliative treatment option for advanced central lung cancer, and its combination with mucosal drug injections also displays potential benefits for those patients who are not suitable for surgery. However, it should be noted that the current study is a single case report. The present protocol provides a new minimally invasive treatment paradigm for advanced TACC, but two limitations should be noted: i) The accumulation of photosensitizers in the skin requires light protection for 4-6 weeks; and ii) local injection requires precise bronchoscopy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

LY, HZ and HW conceptualized the study. LW, LY and HZ designed the study, and collected and analyzed the data. LY, LW, HZ and HW wrote and edited the manuscript. HZ and HW confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present case report has been approved by the Ethics Committee of Dongzhimen Hospital affiliated to Beijing University of Chinese Medicine (approval no. 2024DZMEC-039; Beijing, China). Ethics approval was required for this case report because it involves the use and publication of confidential patient data, including treatment-period photographs.

Patient consent for publication

The patient provided written informed consent for the publication of the medical data and images.

Competing interests

The authors declare that they have no competing interests.

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