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Laryngeal Adenoid Cystic Carcinoma-A Case Report and Review of Literature

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Abstract

Objectives: Adenoid Cystic Carcinoma (ACC) is an extremely rare malignant neoplasm of the glandular tissues. In this article, we present a case of ACC in the larynx along with its clinical, pathological and therapeutic aspects.

Methods: A 53-year-old man presented with suspected laryngeal ACC. Diagnostic tests were performed, including computed tomography and magnetic resonance imaging. Due to its clinical advancement, T4aN0 was qualified for surgical treatment.

Results: Complete laryngectomy was performed with removal of the lobe of the thyroid on the right and selective cervical lymph node removal on the right, and formation of a tracheopharyngeal fistula with implantation of a voice prosthesis. Due to the type of malignant tumor and the degree of local advancement, the patient underwent complementary radiotherapy to the area of the laryngeal bed and regional lymph nodes, bilaterally. Twenty-four months after surgery, the patient remains disease-free.

Conclusion: ACC constitutes less than 1% of all head and neck tumors. It is a highly aggressive malignancy with a high rate of recurrences and a tendency towards distant metastases. Currently, surgical resection with adjuvant radiotherapy is the gold standard in ACC treatment. Long-term follow up is required in ACC patients.

Keywords: Laryngectomy • Laryngeal cancer • Rare malignant neoplasm in the larynx

Introduction

Adenoid Cystic Carcinoma (ACC) is a sporadically occurring malignancy originating from the epithelium, most commonly developing within the salivary glands [1]. In 1859 Billroth first used the term "cylindroma" to describe histological lesions of four salivary gland tumors. The term had been widely used until 1953 when Foote and Frazell changed it into adenoid cystic carcinoma [2].

Malignant tumors of minor salivary glands are rare. It is estimated that they constitute 2%-4% of all malignancies within the neck and head. As regards the larynx, they make up less than 1% of all diagnosed tumors. They are most commonly located in the oral cavity, especially on the hard palate, sporadically in the nasal cavity, paranasal sinuses, pharynx and larynx, which is associated with the distribution of minor salivary glands in those areas [3].

Salivary glands are located submucosally in the mucous membrane of the larynx. The majority of them are situated within the subglottis [60%], but they may also be found in the laryngeal ventricle and epiglottis (vestibular folds, aryepiglottic folds, the petiole of the epiglottis). Since the lesions develop submucosally, they are usually diagnosed at an advanced stage as large tumors [4].

The etiology of ACC remains unknown. It mostly occurs between 50 years and 80 years of age with no sex predilection [1]. The clinical picture is characterized by slow growth, local recurrences, nerve infiltration and the occurrence of distant metastases [2].

The present paper includes a case report of a patient with laryngeal adenoid cystic carcinoma and a concise review of professional literature. Special attention was paid to clinical, pathological and therapeutic aspects.

Case Report

A53-year-old man was referred to the Department of Otorhinolaryngology, Head and Neck Surgery of the University Clinical Center of the Medical University of Warsaw (UCC MUW) in May 2018.

The patient had episodes of hemoptysis, so in March 2018 he underwent Computed Tomography (CT) of the chest and neck. An abnormal tissular lesion of 24 mm × 21 mm × 22 mm with the thickening of the tracheal wall and narrowing of its lumen was located in the subglottal cavity and the upper segment of the trachea on the right. The lesion was adjacent to the right thyroid lobe and the esophagus and the structures might have been infiltrated (Figure 1). Additionally, solitary nodules with the diameter of<3 mm were visualized in the right lung and emphysematous changes were present in the superior lobes of both lungs. Fibrosis was noted in the lungs, mostly in the inferior lobes. The patient had a lymph node sized 22 mm × 12 mm in the hilum of the right lung. There were also several paratracheal lymph nodes measuring 14 mm × 7 mm.

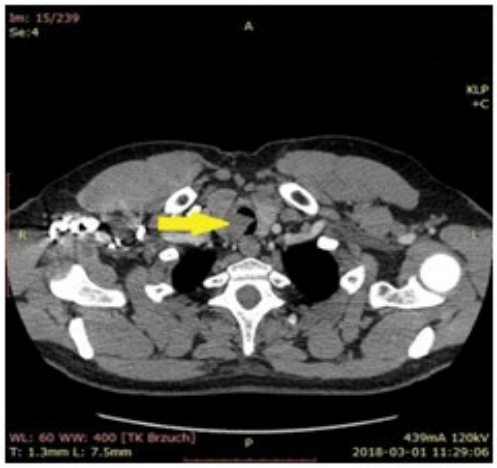

Figure 1. Axial CT of the chest and neck demonstrating an abnormal lesion located in the subglottal cavity on the right (the yellow arrow).

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To perform accessory diagnostic tests the patient was admitted to the Department of Pulmonology of the local hospital. The patient complained of a 4-month history of hoarseness and episodes of hemoptysis for 3 months. Moreover, he admitted to smoking cigarettes for over 30 years. The patient did not suffer from any chronic diseases. His family history was uneventful. During hospitalization, the patient underwent bronchoscopy which revealed a cauliflower-like tumor directly adjacent to the subglottal segment of the larynx which caused tracheal narrowing by approx. 50%-60%. Tumor biopsy was suggestive of carcinoma adenoides cysticum. Spirometry showed normal ventilatory reserves.

In April 2018 the patient obtained a Cancer Diagnosis and Treatment Card and was referred to the Laryngological Clinic of the UCC MUW. The diagnostic work-up was extended by the contrast-enhanced magnetic resonance of the neck. The test revealed a contrast-enhanced pathological area measuring approx. 24 mm × 28 mm × 24 mm in the subglottal area of the larynx, on the right, directly below the cricoid cartilage. The lesion protruded into the trachea, narrowed its lumen, involved the tracheal cartilage laterally and was adjacent to the lobe of the trachea. The border between the tumor and the thyroid was partially indiscernible and a minor infiltration of the right lobe could not be ruled out. Superiorly, the tumor was adjacent to the cricoid cartilage with the suspicion of an infiltration of the posterolateral segment of the cricoid cartilage. Numerous cervical lymph nodes were visible. Their maximum size was 10 mm × 12 mm (IIA level on the left), 8 mm × 17 mm (IIA on the right) and 10 mm × 20 mm (IB).

After admission to the Department of Otorhinolaryngology, Head and Neck Surgery of the UCC MUW the patient underwent indirect laryngoscopy which revealed a tumor located under the right vocal fold (Figure 2). Then, direct laryngoscopy was performed with a flexible endoscope which confirmed the impaired mobility of the right vocal fold. The lymph nodes were not enlarged. After preparing the patient complete laryngectomy was performed (Figure 3). It involved the removal of the lobe of the thyroid on the right and selective cervical lymph node removal on the right. A tracheoesophageal fistula was created and Provox 8,0 voice prosthesis was implanted. A histopathological examination was performed intraoperatively. It confirmed the diagnosis made earlier. The perioperative period was uneventful. The patient was discharged home on day 14 after the surgery.

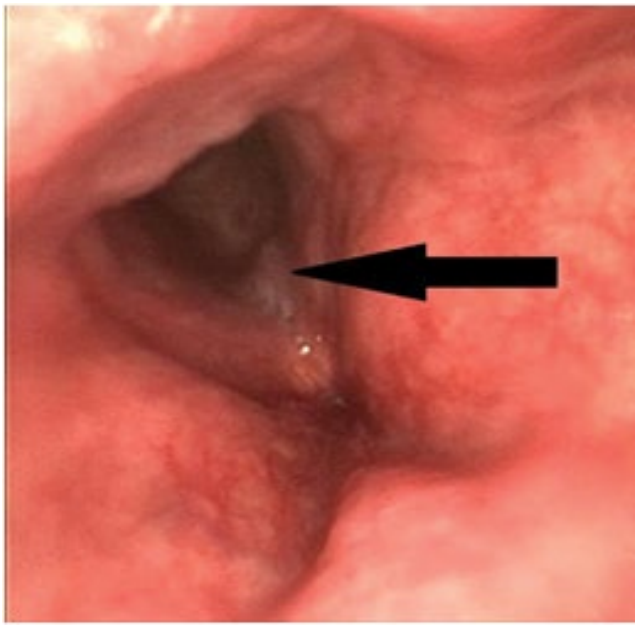

Figure 2. The direct laryngoscopy-the black arrow points a tumor located under the right and left vocal fold.

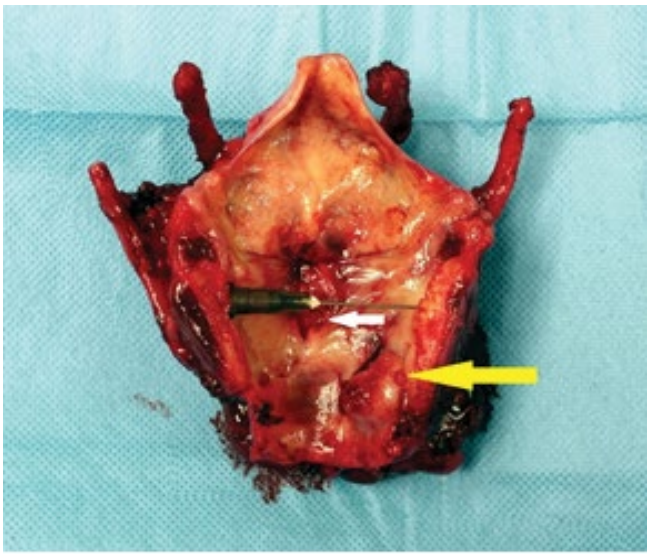

Figure 3. Postoperative view of the larynx with the ACC (the white arrow points linear ulceration with an ACC infiltration; the yellow arrow points an exophytic mass with an ACC).

The histopathological examination of the removed larynx revealed carcinoma adenoides cysticum, with the solid structure constituting 30% (high-grade carcinoma). The tumor of the subglottal area consisted of cribriform and tubular structures and minor solid areas. The features of neuroinvasion were present. The infiltration comprised the adipose tissue of the subglottal area, penetrated the thyroid parenchyma, involved the cartilage and penetrated the perichondrium causing the ulceration of the mucous membrane surface. Finally, tumor progression was described as pT4aN0M0 op R1 according to AJCC 8th Edition Cancer Staging Form.

The patient was qualified for adjuvant radiotherapy because of the type of malignancy and the degree of local progression. The treatment was applied to the tumor bed in the laryngeal area and regional cervical lymph nodes bilaterally. The patient underwent Image-Guided 3D Teleradiotherapy (IGRT) with dose intensity modulation (3D-RotIMRT). The total dose was 70.0 Gy delivered at a fraction dose of 2.0 Gy (35 fractions over 48 days). The groups II-IV of cervical lymph nodes were irradiated bilaterally with a total dose of 54.0 Gy at 1.8 Gy fractions.

Follow up examinations have not revealed a recurrence so far.

Result

Adenoid cystic carcinoma constitutes 10%-12% of all salivary gland tumors and 3%-5% of head and neck tumors. Its general incidence is estimated at 3-4.5 cases per million annually [5]. It is mostly located in the minor and major salivary glands. ACC constitutes less than 1% of all diagnosed tumors in the laryngeal area. Other ACC locations are the tongue, paranasal sinuses, hard palate, nasopharynx, lacrimal glands and external auditory meatus. ACC may also develop in secretory glands located in other tissues, such as the tracheobronchial tree, esophagus, breasts, lungs, prostate gland, uterine cervix, Bartholin's glands and the vulva [6]. As regards the distribution of the salivary glands in the larynx ACC occurs in the subglottis (60%), epiglottis (35%) and glottis (5%) [7].

Its etiology remains unclear. Notably, in the case of squamous cell carcinoma over 90% of patients are smokers. From 50%-60% of patients admitted to smoking in a group of patients with tumors of the minor salivary glands [8]. According to some authors, a slight dominance of females was noted, but the majority of researchers agreed that no sex predilection was observed [9]. ACC is characterized by specific biological features:

infiltrating growth, predisposition for perineural invasion and hematogenous dissemination. Metastases to cervical lymph nodes are rare, but late recurrences with distant metastases are common [4].

Macroscopically, ACC presents as an asymmetrical, slowly growing, hard, a solitary lesion with an incomplete or no capsule, frequently characterized by invasiveness with adjacent tissues [5]. Dardick hypothesized that ADD, which is currently defined as a basaloid tumor, originated from specific segments of a ductal-lobular unit. The hypothesis has recently been confirmed [10,11]. Microscopically, ACC consists of non-luminal basal epithelial cells, haematoxylin-stained, with scanty cytoplasm and the limited pleomorphism of small cellular nuclei. This type of tumor presents mainly myoepithelial differentiation [12].

Histologically, three types of ACC are differentiated: tubular, cribriform and solid. However, the histological structure usually presents a combination of those [1,13]. The dominant pattern determines the category of lesion. Cribriform tumors are the most common. They are composed of basaloid cells organized in oval masses, various in size with the presence of oval cyst-like spaces. Tubular tumors are characterized by the presence of luminal cells organized in tubular structures surrounded by non-luminal cells with clear cytoplasm. The solid pattern is composed of basaloid cells growing in sheets without free spaces [5]. Currently, two systems of prognosis qualification are used: with the cut-off value for the solid pattern>30% according to Szanto and>50% according to Spiro [14,15]. Szanto et al. distinguished the following malignancy grades: grade I (well-differentiated)-mostly tubular and cribriform pattern, no solid component; grade II (moderately differentiated)-cribriform pattern only or a combination of all forms with the solid component of>30% of tumor mass; grade III-mostly solid pattern [14] (Table 1). In the present case, the tumor included cribriform, tubular and minor solid structures. Histopathological examination is the basis of making an accurate diagnosis and determines further management.

Table 1. Definitions of grading systems of ACC.

Grade	Szanto et al. [14]	Spiro et al. [15]
I	predominantly tubular, no solid	mostly tubular or cribriform, occasional solid
II	predominantly cribriform, a combination of all forms with<30% solid	mixed with>50% substantial solid
III	solid component>30%	only solid

Occasionally, it is necessary to use immunohistochemical markers to confirm ACC. Myoepithelial cells of the tumor demonstrated the expression for mesenchymal markers (smooth muscle actins, smooth muscle myosin heavy chains, s100 protein) and vimentin. The presence of biomarkers, such as c-KIT, VEGFR (vascular endothelial growth factor), Ki67 and p53 was associated with greater tumor malignancy and poorer prognosis. The use of immunohistochemical markers is significant when verifying the diagnosis and it has prognostic value as regards the course of the disease [5].

Contrast-enhanced CT and MRI are other important elements in preoperative assessment. They facilitate the determination of the primary tumor location, its progression and dimensions, and distant metastases [9,16]. Computed tomography scanning is preferred in the assessment of osseous lesions, while magnetic resonance is useful in the evaluation of local progression in the soft tissues, metastases to cervical lymph nodes and bone marrow infiltration [16]. Moreover, MRI examination is the gold standard in the follow up after treatment. A full-body CT and 18F-FDG PET may be used to detect distant metastases, especially for staging and treatment monitoring [17].

The manifestations depend on the location and progression of the tumor. Due to the slow and submucosal development of ACC, patients may initially manifest no specific symptoms [18]. At later stages, they develop airway narrowing with dyspnea, cough, hoarseness, pharyngeal pain, and hemoptysis [19]. The subglottal location predisposes to dyspnea (due to airway narrowing), while glottal or epiglottal involvement is more commonly associated with hoarseness (due to the pathology of vocal cords) [3]. Pain and paresthesia may be reported in the case of perineural infiltration [6]. The present patient reported hoarseness and episodes of hemoptysis.

The management of laryngeal ACC is still the subject of discussion due to its low occurrence rates [20]. Surgical resection combined with adjuvant radiotherapy remains the method of choice. It is commonly required to perform complete laryngectomy with a wide margin of resection because of the associated risk of submucosal proliferation, the infiltration of nerves and lymphatic vessels. Partial laryngectomy is possible in selected patients who have a small, well-demarcated tumor and oncologically-negative margins of resection [20]. Radical neck dissection is implemented in cases with confirmed metastases to regional lymph nodes [21].

It was demonstrated that postoperative radiotherapy was associated with tumor regression and symptom alleviation [7]. Radiotherapy should be considered as the sole modality if surgery is impossible. Balamucki et al. studied a group of 46 patients treated with radiotherapy only. They reported that 36% of patients remained free of recurrences over a 10 year follow-up [22]. Furthermore, radiation therapy is a standard treatment in the case of metastases to the brain or bones [23].

ACC is characterized by slow growth, so it does not present a satisfactory response to systemic chemotherapy. Nevertheless, the influence of chemotherapy on the course of the disease has been studied for the past few years. The results consistently demonstrated a low therapeutic response to cytotoxic doses [6]. Currently, chemotherapy is used in palliative therapy in patients with advanced disease, metastases or rapid progression of the disease, who may not be qualified for operative treatment or clinical trials [24].

The latest research concentrated on distinguishing and determining the molecular and hormonal profile of the tumor to develop a targeted treatment. ACC is most commonly characterized by the transmembrane receptor coded by the c-KIT gene associated with the regulation of cell migration, differentiation and proliferation. The analysis of numerous markers revealed the overexpression of c-KIT in 90% of ACC cases. The reported frequency of EGFR (epidermal growth factor receptor) overexpression varied in ACC from 0%-37%, which suggested the potential effectiveness of anti-EGFR treatment [25].

Compared to other neoplasms ACC is characterized by slower growth and lower tendency towards disseminating to local and regional lymph nodes. Nevertheless, ACC was described as one of the most destructive and unpredictable malignancies of the head and neck [26]. The resection of the primary tumor is quite commonly followed by both local recurrences and distant metastases. It reflects the tendency towards tumor dissemination along neural pathways, extension beyond surgical margin and hematogenous dissemination [6]. Distant metastases develop in about 40% of ACC patients. The risk factors include solid tumor pattern, size >3 cm, local lymph node involvement [27]. The most common locations of distant metastases are the lungs, followed by bones, the liver, skin, breasts and the brain [28]. Intracranial disease development is rare. It results from direct tumor proliferation or perineural invasion rather than hematogenous dissemination [29]. The occurrence of metastases indicates the advanced stage of the disease and markedly affects the prognosis. Patients with metastases limited to the lungs were characterized by higher survival rates than those with metastases to bones or other organs [30].

The prognostic factors depend on tumor location, its progression and microscopic structure. The unfavorable factors include age over 60, solid tumor type, advanced clinical stage and the presence of neuroinvasion [1,3]. Our patient was diagnosed with a moderately locally advanced tumor (T4a, N0, M0) with the infiltration of adjacent adipose tissue and the thyroid, and neuroinvasion (T4a). The resected cervical lymph nodes included no neoplastic cells (N0). Moreover, no distant metastases were observed (M0).

Therefore, long-term follow-up is necessary for patients. In the present case the follow-up of 24 months revealed no recurrences or metastases.

Conclusion

Adenoid cystic carcinoma occurs relatively infrequently and constitutes less than 1% of all head and neck tumors. Laryngeal ACC predominantly develops in middle-aged patients. It is characterized by slow growth with dyspnea being the most common symptom. It is a highly aggressive malignancy with a high rate of recurrences and a tendency towards distant metastases. Currently, surgical resection with adjuvant radiotherapy is the gold standard in ACC treatment. Long-term follow up is required in ACC patients.

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Conflict of Interest

The authors declare that there is no conflict of interest.

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