CASE REPORT

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Synchronous laryngeal cancer

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Abstract

Multiple primary cancers are usually defined as primary malignant tumors of different histological origins in one person. Synchronous cancers are defined as two or more primary cancers diagnosed in the same patient at the same time or within six months after identifying the first tumor, and those cancers that develop at more than a six-month interval are termed as metachronous multiple primary cancers. Our study comprised of a patient with synchronous laryngeal cancer with double localizations. The case was solved through surgical excision of the tumors. Histopathological and immunohistochemistry examinations revealed synchronous laryngeal cancer. Laryngeal cancer should usually be managed through surgical resection, followed by oncological treatment.

Keywords: larynx, synchronous cancer, total laryngectomy, histopathology, immunohistochemistry.

Introduction

Laryngeal cancer comprises up to one third of all head and neck cancers, being the second most common cancer within the head and neck, making it an important cause of morbidity and mortality. It may involve various laryngeal localizations, influencing the presentation signs and symptoms, dissemination, and treatment options [1, 2]. Given the involved site and associated symptoms, as well as patient background, history of smoking and alcohol use, level of education and socio-economic status, patients will approach their physician in the early or late stages of the disease. Given the stage of the disease, certain functions of the larynx may be altered, such as respiration (breathing), deglutition (swallowing), phonation, and at times taste and smell [3].

Most laryngeal cancers are squamous cell carcinoma (SCC), comprising of up to 95% [4, 5]. Most are well-differentiated SCC, while others represent squamous cell variants (verrucous, sarcomatous, neuroendocrine carcinomas) [1].

Synchronous cancers consist of two or more malignant tumors diagnosed within the same patient at the same time. They are rarely encountered, even less within the same organ [5].

Aim

The paper is aimed at presenting the case of two synchronous malignant tumors situated within the larynx and a review of the literature.

Case presentation

We present the case of a 59-year-old male patient, admitted to the Ear, Nose and Throat (ENT) Clinic of the Emergency County Clinical Hospital of Craiova, Romania, for persistent dysphonia (hoarseness) and progressive dysphagia over the past three months.

The patient had a medical history of type 2 diabetes, with right lower limb amputation, hyperuricemia, chronic ischemic cardiomyopathy, hypertension accompanied by high cardiovascular risk. The patient was a heavy smoker: 44 years with more than 20 cigarettes/day and had a history of alcohol use, especially beer and wine.

Physical examination revealed small cervical lymphadenopathy upon inspection and palpation, both on the right and left sides of the neck.

On clinical examination, indirect laryngoscopy revealed two tumoral masses, one located on the laryngeal face of the epiglottis, and one situated in the left hemilarynx.

Patient assessment was continued through flexible white light (WL) panendoscopy, which revealed a tumor of approximately 2.3 cm in diameter situated on the posterior face of the epiglottis, within the right hemiepiglottis and slightly expanding over the edge of the epiglottis; and a second, synchronous laryngeal tumor of 1.7/1.3 cm involving the left vocal fold and Morgagni ventricle. The movement of the left vocal cord was severely impaired (Figure 1).

Biological exams revealed hyperglycemia of 133 mg/dL, for which a specialist examination was requested and concluded to continue with a recommendation of oral antidiabetics.

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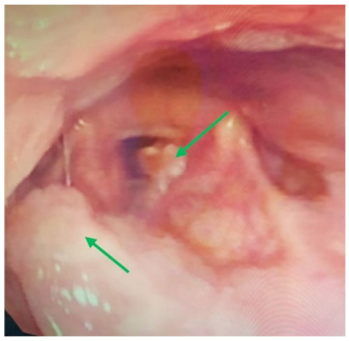

Figure 1 – ***Flexible white light panendoscopy revealed two tumoral masses, one located on the laryngeal face of the epiglottis, and one located within the left hemilarynx.***

Chest radiograph was performed and was normal.

Cervical ultrasound echography described a right cervical lymph node (CLN), with 18/9 mm in diameter and a left CLN, with 21/10 mm in diameter.

Both biopsies, taken under suspended laryngoscopy from the two tumors, indicated SCC.

A multidisciplinary oncological tumor board was held to discuss the treatment plan for this patient with two cancers in the same organ – larynx, on top of quite a few comorbidities. It was decided that the patient undergo surgical resection of the tumor, followed by oncological treatment.

The patient underwent total laryngectomy with selective bilateral neck dissection (Figures 2–4).

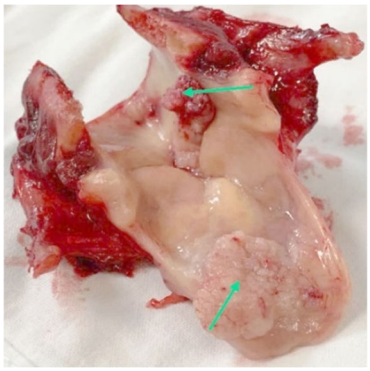

Figure 2 – ***Larynx after total laryngectomy, with a vegetant tumor situated on the laryngeal face of the epiglottis, and a second tumor situated on the left hemilarynx in the back.***

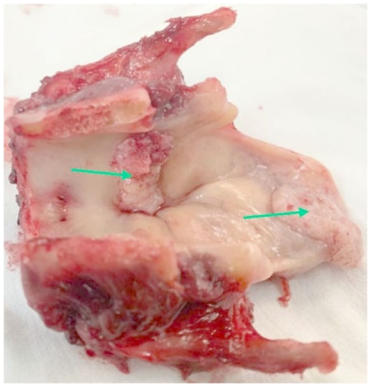

Figure 3 – ***Larynx after total laryngectomy, with one tumor situated on the left hemilarynx involving the left vocal cord, Morgagni ventricle and subglottic region; a second tumor is situated on the laryngeal face of the epiglottis.***

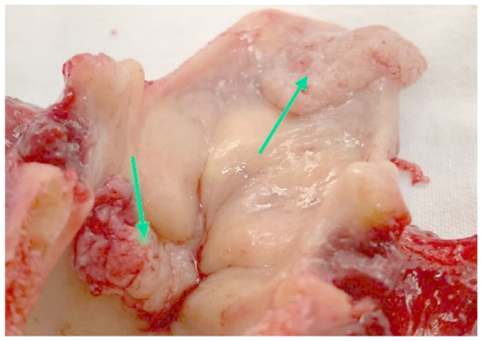

Figure 4 – ***Larynx after total laryngectomy with synchronous laryngeal cancer, with double localization, left hemilarynx and epiglottis. The distance between the tumors is about 3.5 cm.***

The surgical excision piece was placed in a 10% neutral buffered formalin solution and sent to the Pathological Anatomy Laboratory of the same Hospital; here, the tumors were embedded in paraffin, sectioned with a microtome at a thickness of 4 μm and stained with Hematoxylin–Eosin (HE). The following antibodies were used for the immunohistochemical (IHC) study: anti-p53 (monoclonal mouse anti-human p53 protein, clone DO-7, 1/50 dilution, Dako); anti-Ki67 (monoclonal mouse anti-human Ki67, clone MIB-1, 1/50 dilution, Dako); anti-cytokeratin 7 (CK7) (monoclonal mouse anti-human CK7, clone OV-TL 12/30, 1/50 dilution, Dako); anti-cluster of differentiation (CD)3 (monoclonal mouse anti-human CD3, clone F7.2.38, 1/25 dilution, Dako); anti-CD20 (monoclonal mouse anti-human CD20cy, clone L26, 1/50 dilution, Dako); anti-CD68 (monoclonal anti-human CD68, clone KP1, 1/100 dilution, Dako); anti-CD34 (monoclonal mouse anti-human CD34 class II, clone QBEnd 10, 1/50 dilution, Dako).

Histopathological analysis

The tumor located at the level of the epiglottis (T1) appeared as a poorly differentiated squamous carcinoma (G3), ulcerated, invading the entire thickness of the chorion and in places, the epiglottic cartilage (Figure 5, A and B).

The tumor consisted of several islands of tumor cells, delimited by a basement membrane and surrounded by a stroma strongly infiltrated by inflammatory cells.

The tumor located in the left hemilarynx (T2) was a moderately differentiated (G2), ulcerated, SCC invading the chorion, associated with areas of tumor necrosis, abundant chronic diffuse inflammation (with lymphoid follicle formation), and discrete paraneoplastic giant cell chronic inflammation (Figure 5, C and D).

The IHC study showed a positive reaction of the anti-p53 antibody in both tumors, which indicates the involvement of the tumor protein p53 (*TP53*) gene in the pathogenic mechanism of tumor development. We mentioned that the IHC reaction was more intense in T1 compared to T2 (Figure 6, A and B).

An IHC reaction was also recorded for the anti-Ki67 antibody; in T1, the IHC reaction was very strong, marking more than 90% of tumor cell nuclei, while in T2 only about 50% of tumor cell nuclei were marked (Figure 7, A and B). In contrast, both tumors were negative for the anti-CK7 antibody, although the normal laryngeal epithelium was stained positive for the anti-CK7 antibody (Figure 8, A and B).

Inflammatory infiltrate was evident in the tumoral and peritumoral stroma of both tumors. The infiltrate was

unevenly distributed and had varying intensities from one area to another of the tumors. Very rarely, we identified lymphoid follicles. Among the cells of the immune system, the most numerous were T-lymphocytes and macrophages (Figure 9, A and B).

Investigating the tumor vascularity using the anti-CD34 antibody showed that both tumors were well vascularized through the development of networks of angiogenesis vessels, predominantly of the capillary type, located in close proximity to the tumor cells (Figure 10, A and B).

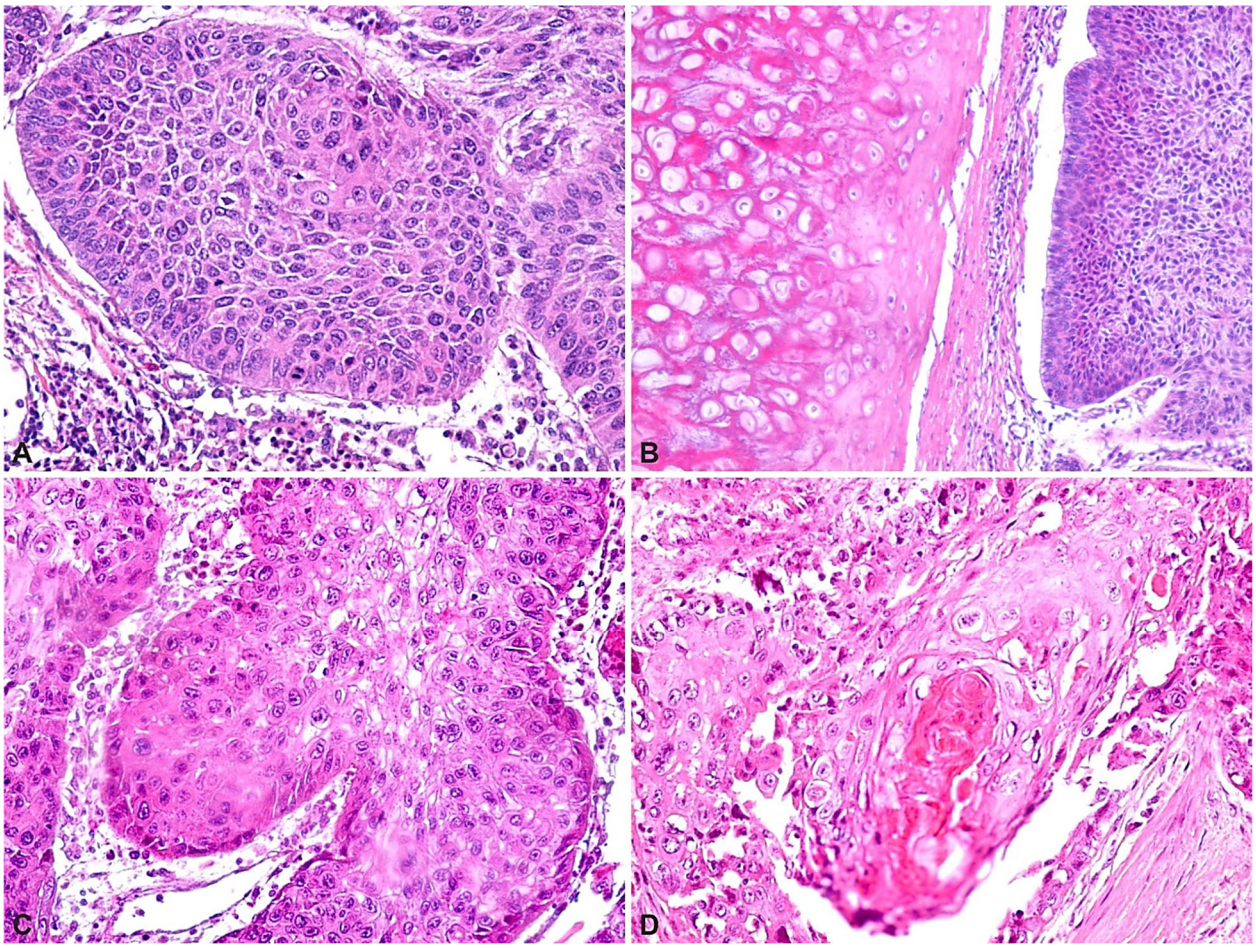

Figure 5 – ***(A) T1: tumor island with numerous cellular and nuclear atypia and with multiple mitoses; (B) T1: area of invasive tumor in the perichondrium of the epiglottic cartilage; (C) T2: image of moderately differentiated SCC; (D) T2: moderately differentiated SCC with formation of "keratotic pearls". HE staining: (A, C and D) ×200; (B) ×100. HE: Hematoxylin–Eosin; SCC: Squamous cell carcinoma.***

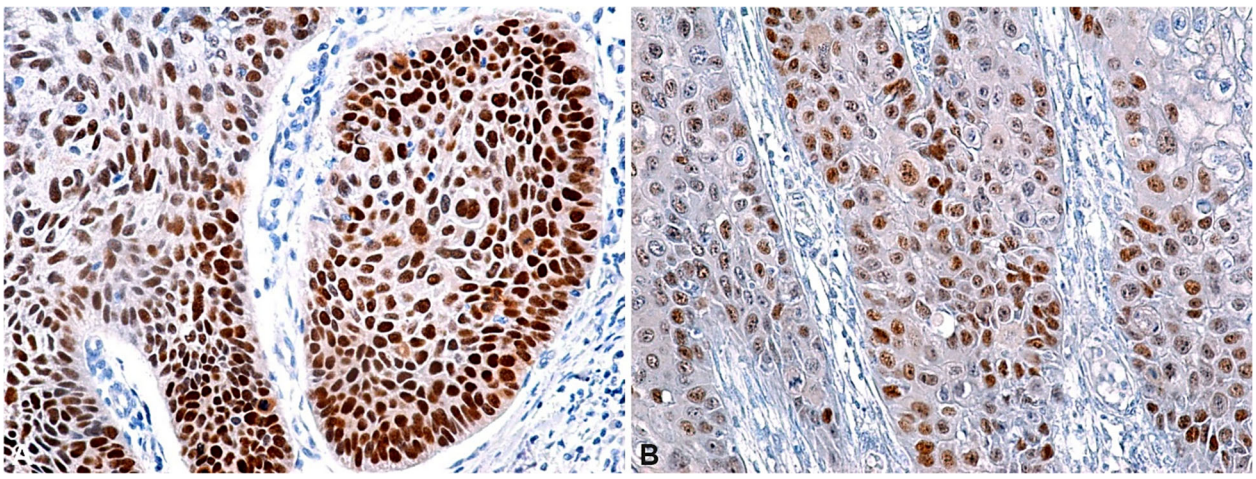

Figure 6 – ***(A) T1: intense positive reaction of the anti-p53 antibody: (B) T2: moderate anti-p53 antibody reaction. Immunolabeling with the anti-p53 antibody: (A and B) ×200.***

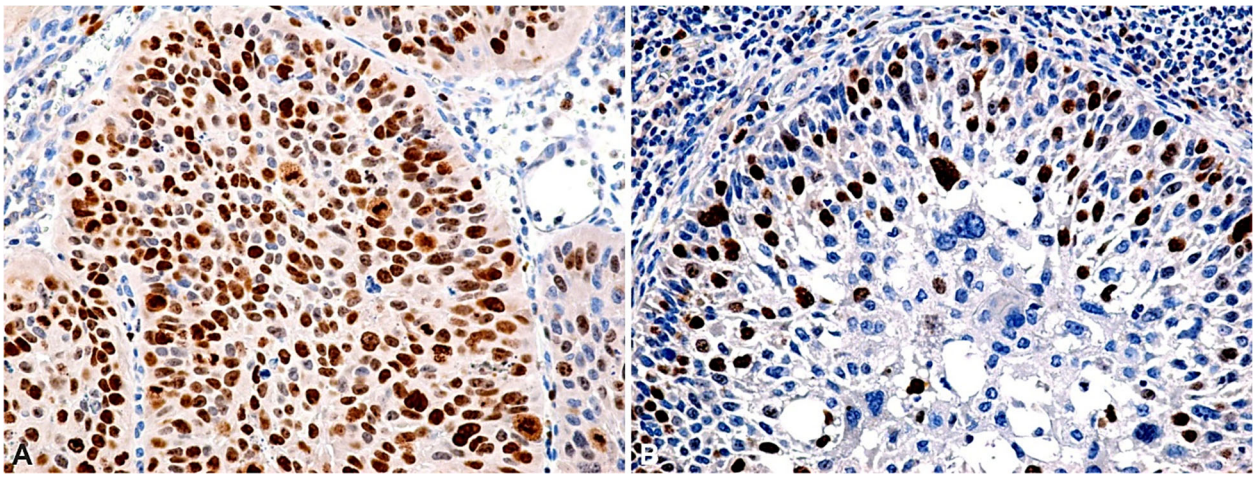

Figure 7 – ***(A) T1: intense positive reaction of the anti-Ki67 antibody; (B) T2: moderate anti-Ki67 antibody reaction. Immunolabeling with the anti-Ki67 antibody: (A and B) ×200.***

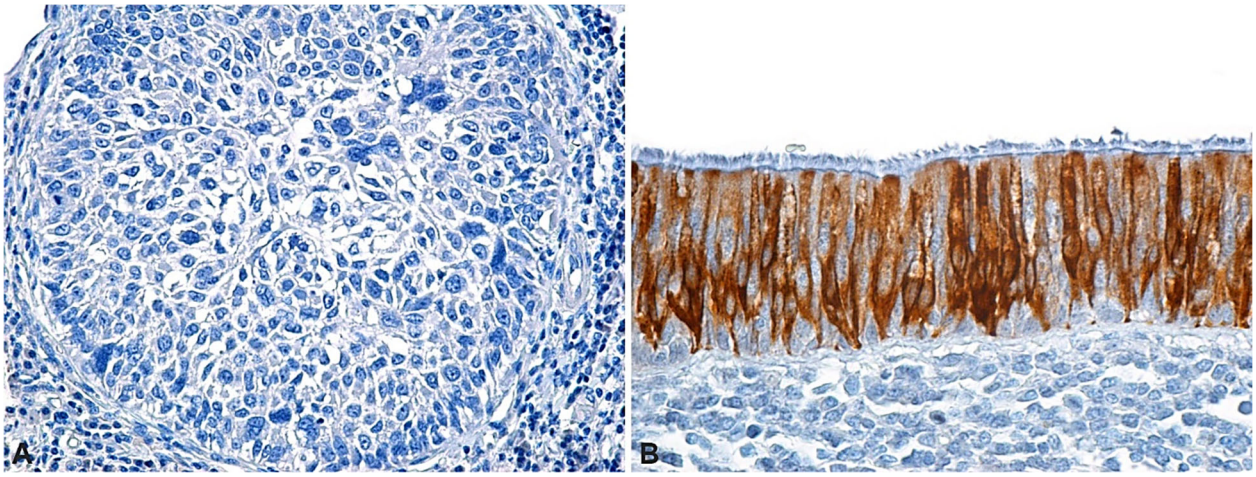

Figure 8 – ***(A) T1 with negative reaction to CK7; (B) Laryngeal epithelium with an intensely positive reaction to the anti-CK7 antibody. Immunolabeling with the anti-CK7 antibody: (A and B) ×200. CK7: Cytokeratin 7.***

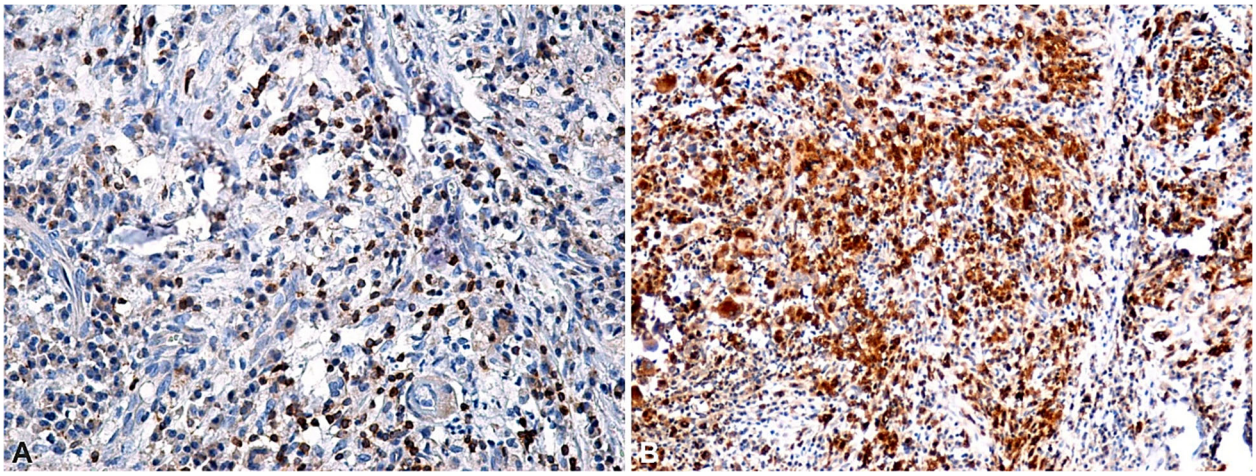

Figure 9 – ***(A) T1: tumor stroma heavily infiltrated with inflammatory cells, mainly T-lymphocytes; (B) An area of tumor stroma infiltrated predominantly with macrophages. Immunostaining with the anti-CD68 antibody: (A and B) ×100. CD68: Cluster of differentiation 68.***

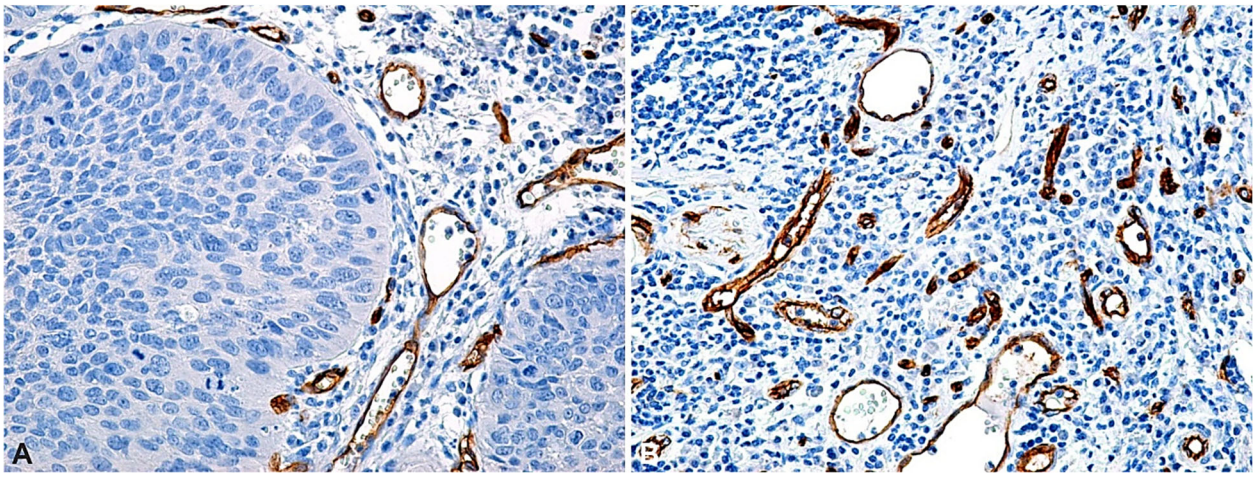

Figure 10 – ***(A) T1: tumor stroma with angiogenesis vessels of varying caliber, mostly arranged around the tumor "islands"; (B) T2: tumor stroma intensely infiltrated with inflammatory cells and numerous angiogenesis vessels. Immunolabeling with the anti-CD34 antibody: (A and B) ×200. CD34: Cluster of differentiation 34.***

In the surgical excision piece, 12 CLNs were identified, that did not have metastases on microscopic examination.

As such, we demonstrated that the patient presented with two simultaneous SCC laryngeal tumors, located in the epiglottis and left hemilarynx.

Postoperative evolution was favorable. The patient underwent oncological treatment consisting of radiotherapy and induction chemotherapy.

Follow-up at one month, three months and every six months after, over the first two years showed no recurrence.

Discussions

Billroth was the first to elaborate criteria for multiple primary tumors dictating that each tumor must have a different histological appearance, arise in different locations, and produce its own metastases. The criteria were, however, very strict; therefore, in 1932, Warren & Gates put forward new criteria, which are still in use and require the following: (*i*) each tumor must be confirmed through histopathological (HP) examination; (*ii*) each tumor must be localized differently, separated, distinct; apart from one another, with healthy tissue in between; (*iii*) the prospect of one tumor being a metastatic lesion of the other needs to be ruled out.

Our case encompasses all these three requirements in order for the tumors to be synchronous.

The definitions and classifications of multiple primary cancers have been proposed by Moertel all the way back in 1977 and hold true to this day. In consequence, group I consists of multiple primary cancers that occur in organs with equivalent histology, group II incorporates multiple primary cancers that originate from disparate tissues and group III comprises of cancers from different types of tissue and organs that coexist with group I cancers, forming multiple primary cancers, consisting of three or more neoplasms. Group I is additionally subdivided into group A, encompassing cancers that occur in the same tissue and organ, group B, comprising of cancers that are from the same tissue and different organs, and group C involving cancers that occur in bilateral organs. Our case falls within the first group, and its subdivision A. Multiple primary neoplasms are also classified as synchronous and metachronous. As such, regarding the moment of diagnosis, if two or more primary tumors are reported as simultaneous, they must be identified concurrent to the primary tumor. Tumors may be synchronous when diagnosed in less than six months of the primary tumor, or metachronous when discovered more than six months after the primary tumor [6–8]. As we are reporting two tumors, in line with the above-mentioned criteria, and that have been diagnosed simultaneously, we are cataloguing them as synchronous.

Simultaneous malignant tumors are uncommon, and as previously stated, postulate the existence of two or more cancers within the same patient at the same time. Since our report is based on laryngeal involvement, we shall focus on simultaneous, synchronous, and metachronous tumors in which at least one of the tumors involves the larynx.

According to previous studies, the rate for reported tumors synchronous with SCC of the larynx ranges from 1% to 10%, and that of metachronous tumors is from 10% to 20%. Rates tend to be higher in men and are influenced by tobacco use and supraglottic localization [5, 9–11]. The current case is therefore encompassed within the 1% to 10% range and is in line with the more common rates of synchronous tumors encountered in the ranks of men and smokers.

Going through the literature, we have observed tumors developing in separate organs, such as larynx and lungs [12], with both synchronous and metachronous SCC; tumors of the larynx and esophagus, identified through HP examination as SCC [13, 14], HP types indictive of chronic exposure to tobacco and alcohol [13, 15, 16], with patients having manifested dysphagia for solids, hoarseness of the voice and cachexia upon examination. Synchronous or metachronous tumors have also been reported in the larynx and liver or kidneys [17, 18], manifesting through dysphonia and dysphagia, with the laryngeal carcinoma usually being identified as a SCC. In the head and neck region, synchronous tumors have been encountered within the larynx and nasopharynx [19], oropharynx, hypopharynx, oral carcinoma [20, 21]. Given all these presentations of synchronous and metachronous tumors, we find our synchronous laryngeal presentation to be of particular interest and in line with usual neoplastic etiology (such as chronic

tobacco and alcohol exposure, as per our case), with signs and symptoms commonly involving tumors of the larynx (dysphonia and progressive dysphagia), accentuated, given the dual tumor involvement over the same area (two tumors in close vicinity and causing similar symptoms).

Simultaneous, synchronous, and metachronous tumors of the larynx have been previously encountered, yet there are few reported cases. They range from different histological types of malignant tumors to simultaneous benign and malignant tumors. There have been reported cases of synchronous tumors of the larynx characterized by concurrent malignant and benign tumors of the larynx, with one particular case of rhabdomyoma and chondrosarcoma of the larynx [22].

In most of the previous cases in literature, the laryngeal carcinoma was mostly a SCC of various differentiation degrees. This is comparable to our case of concurrent SCC of the larynx, having identified both tumors as SCC with distinct differentiation degrees. In our case, the patient had synchronous laryngeal SCC of which one tumor was poorly differentiated and the other moderately differentiated.

Regarding HP types of simultaneous, synchronous, or metachronous laryngeal carcinomas, a study of literature revealed occurrences of chondrosarcoma and an epidermoid carcinoma *in situ* involving both vocal cords [23], SCC and leiomyosarcoma involving both the vocal cords and the anterior commissure managed through partial laryngectomy [7].

Most clinical manifestations of disease were like those form single site laryngeal tumors and manifested generally through hoarseness and dysphagia, in close regard to tumor size and localization.

Tumor location and HP type, as well as tumor stage determine the available treatment options. For this, WL nasopharyngeal endoscopy is mandatory to assess tumor location and extension into neighboring structures. It is to be followed by imaging to better appreciate the depth of its extension and biopsy to establish histological types and organize treatment plans – surgical and oncological.

In the specialty literature, there are reports of synchronous or metachronous laryngeal malignancies, most of which have SCC as one of the tumor types, while the other tumor can be an adenocarcinoma, leiomyosarcoma, chondrosarcoma, histiocytoma. Studies also report an increased risk of developing synchronous tumors in the head and neck region [24], especially for patients with laryngeal SCC [25, 26]. The majority of patients were treated using surgery and radiotherapy, as per the current case presented in this report [5, 27].

The incidence of head and neck cancer is increasing. To improve the survival of head and neck cancer patients, an effective program of screening and/or chemoprevention of second malignancies is essential.

Conclusions

Second primary malignancies are an important cause of death in survivors of head and neck SCC. Synchronous primary malignancies pose a significant clinical interest because they can be identified by screening procedures at the time of diagnosis. Synchronous multiple malignancies of the larynx are very uncommon. We report a case with double laryngeal cancer: a moderately differentiated SCC, with simultaneous poorly differentiated SCC, which was confirmed with HP and IHC examination. Fortunately, surgical treatment was applied to both tumors at the same time. An effective program of screening of second malignancies is essential for patients with head and neck cancer.

Conflict of interests

The authors declare no conflict of interests.

Institutional Review Board Statement

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Emergency County Clinical Hospital of Craiova, Romania.

Informed Consent Statement

Written consent for the publication of pictures and personal information was obtained from the patient described in this case report.

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