

## CASE REPORT

## Acinic cell carcinoma of minor salivary glands – case report

CAMELIA LIANA BUHAȘ<sup>1,2)</sup>, ELENA ROȘCA<sup>3)</sup>, GABRIELA MUȚIU<sup>1)</sup>, ALINA CRISTIANA VENTER<sup>1,3)</sup>,  
 BOGDAN ADRIAN BUHAȘ<sup>3)</sup>, RĂZVAN COUȚI<sup>4)</sup>, CAMELIA FLORENTINA CIOBANU<sup>1)</sup>, DRAGOȘ MIRCEA ROȘCA<sup>3)</sup>

<sup>1)</sup>Department of Morphological Disciplines, Faculty of Medicine and Pharmacy,  
 University of Oradea, Romania

<sup>2)</sup>Forensic Service of Bihor County, Oradea, Romania

<sup>3)</sup>Department of Urology, Emergency County Hospital, Oradea, Romania

<sup>4)</sup>Department of Urology, Emergency County Hospital, Cluj-Napoca, Romania

### Abstract

Salivary gland tumors have a high incidence (90%) within the parotid gland. The acinic cell carcinoma (ACC) represents only 1–3% of the salivary gland tumors, most frequently affecting the parotid. The minor salivary glands rarely develop ACC and when the ACC is localized in these glands, generally, it has a less aggressive evolution. The main criterion in the diagnostic of ACC is the histological examination with the regular Hematoxylin–Eosin (HE) staining and additionally Periodic Acid–Schiff (PAS) special staining. Immunohistochemical (IHC) examination confirms the origin of the tumor cells and the cellular proliferation index. Therapeutic management consists of surgical excision and radiotherapy. Left jugular tumor was the clinical diagnosis in the case we presented. The computed tomography (CT) examination revealed a voluminous expansive process of the left cheek. Surgery was performed with tumor resection and the skin defect was threatened. The histopathological (HP) and IHC exams have established the diagnosis of minor salivary glands adenocarcinoma with increased tumor proliferation index. The evolution was unfavorable to tumor recurrence in a short time of one year.

**Keywords:** acinic cell carcinoma, PAS staining, CK, CEA, p53, Ki67.

### Introduction

The salivary gland acinic cell carcinoma (ACC) is a rare malignant tumor. It represents 6–10% of the total malignant tumors of these glands [1, 2]. It is rarely localized in the minor salivary glands located at the base of the tongue; the predisposed location on the head and neck is in the parotid gland [3, 4]. According to the literature data, the ACC originates in the parotid in 81–98% of the cases, in the submandibular glands in 11% of the cases, and in the minor salivary glands in 3–12% of the cases [5]. The tumor is most frequently diagnosed in females, in 58.8% of the cases, in comparison to males, where the percentage is just 41.2% [1, 6]. The average age of females diagnosed with this tumor is about 30 years old [1, 6]. Risk factors are radiation exposure, and genetic predisposition [7]. Working in certain industries like rubber, wool, automobiles, textiles, cosmetics or exposure to metals which contain lead, asbestos, nickel, increases the incidence of this tumor among the employees [8]. Other risk factors are certain viruses (*e.g.*, Epstein–Barr virus) [8]. The clinical aspect can be observed as an enlargement of the parotid gland volume, rarely as an enlargement in the volume of the regional lymph nodes. The diagnosis is established based on histopathological examination of the tissue fragments collected through aspiration, punch biopsy or histopathological examination of the excised tumor.

We present a rare case of ACC that has several distinct features: an elderly male, smoker and alcoholic, with a tumor located in the small salivary glands of the oral mucosa (left cheek), paraclinical [computed tomography

(CT), radiography (X-ray)] diagnosed as a cystic form with a cytological examination of large-negative secretion, with a certain diagnostic of histopathologically established ACC, which after the first surgery has an evolution towards relapse over a year.

### Case presentation

The authors present the case of a 73-year-old male, B. J., from the rural area, smoker and chronic alcohol consumer, without a specific medical history, who undergoes an oral and maxillofacial surgery in the Clinic of Oral and Maxillofacial Surgery, Emergency County Hospital, Oradea, Romania, for a tumor formation on the left side of the face (according to the Observation Sheet No. 2314/18.01.2016). The clinical examination and CT establish the diagnosis of cystic tumor formation. The CT shows a voluminous expanding mass with the axial diameter of 48/88 mm, located on the left cheek, deforming the skin, which covers the superior and inferior left maxillary, with irregular margins, multi-lobulated, but relatively well delimited, with heterogeneous structure, parenchyma areas, and other areas of para-fluid density; the largest of the para-fluid lesions was located on the posterior side of the tumor formation of approx. 40/54 mm. Contrast substance was intravenously administered and a relatively intense grip is shown in the parenchymatous areas. The diagnosis was established: voluminous expanding mass of the left cheek region. The repeated cytological examination from the large quantity of secretion was negative. A punch biopsy was performed from the tumor formation for the histopathological examination. The histopatho-

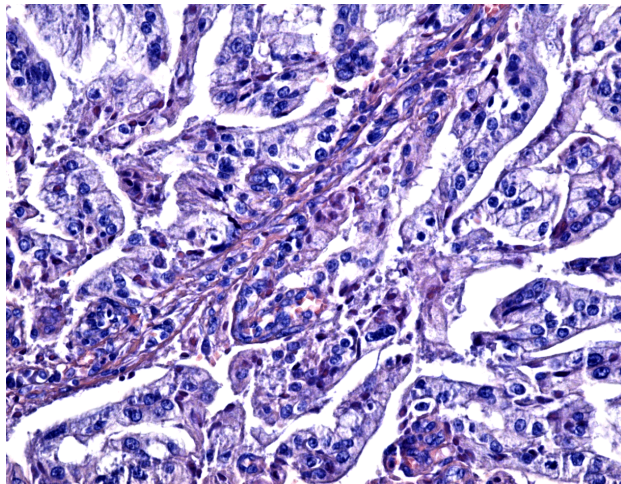
logical examination with Hematoxylin–Eosin (HE) and Periodic Acid–Schiff (PAS) stainings show papillary structures coated by one or more cellular layers with secreting aspect, containing “zymogen granules”, which are PAS positive (Figure 1), micro-cystic areas, hemorrhagic areas, and atypical rare mitoses (less than 5/10 high-power field); on HE staining, there are no obvious myoepithelial cells and intermediary cells (Figures 2–5). The aspect indicates a minor salivary gland low-grade adenocarcinoma (acinar vs. papillary). The immunohistochemical (IHC) investigations point out that anti-carcinoembryonic antigen (CEA) and anti-epithelial membrane antigen (EMA) were positive. Cyclin and human BRCA1 gene mutation were focal positive on the tumoral cells. B-cell lymphoma-2 (Bcl-2) was positive on the solid component and this fact can indicate the existence of neuroendocrine component of the tumor. Ki67 antigen (Ki67) was positive in over 65% of the tumoral cells (Figures 6–10), while p53 protein and p63 protein were negative. The tumor was surgically removed, and the patient undergoes oncological radiotherapy. After a year, the patient returns to the Department of Surgery with a

relapsing tumor. A tumor of much smaller dimension was found, with an ulceration of the cheek skin and an exophytic growth. Palliative surgical intervention was performed and for esthetic purposes, the patient was redirected to the Department of Oncology. The paraclinical examination in the Department of Oncology did not show secondary tumor determinations (Figure 11).

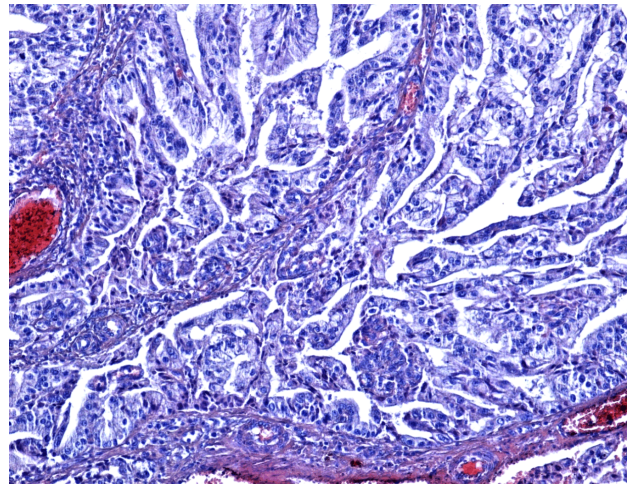
## Discussion

The malignancy of this tumor has been controversial in the past. Some publications classified ACC as a benign adenoma or an acinic cell tumor. Recent literature has demonstrated the relapsing potential of this tumor and its potential for metastasis and death. This fact determined the *World Health Organization* (WHO) to reclassify this tumor and include it in the “malignant carcinoma” category [8].

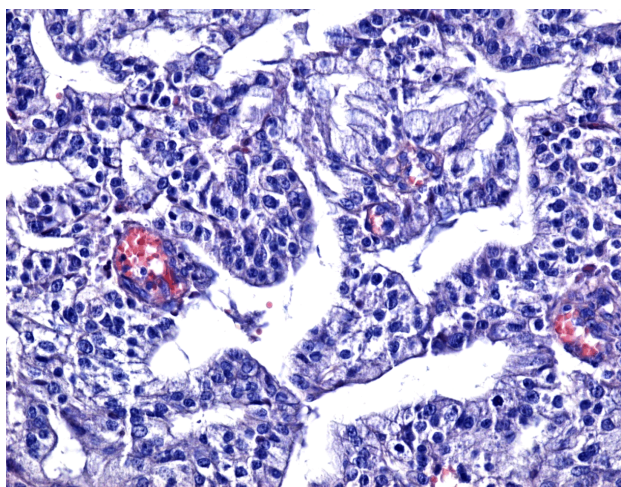
ACC is considered a high frequency tumor in the female population up to 52 years old (the average age being 30 years old). In the presented case, the age and gender are atypical, the patient being a 73-year-old male.



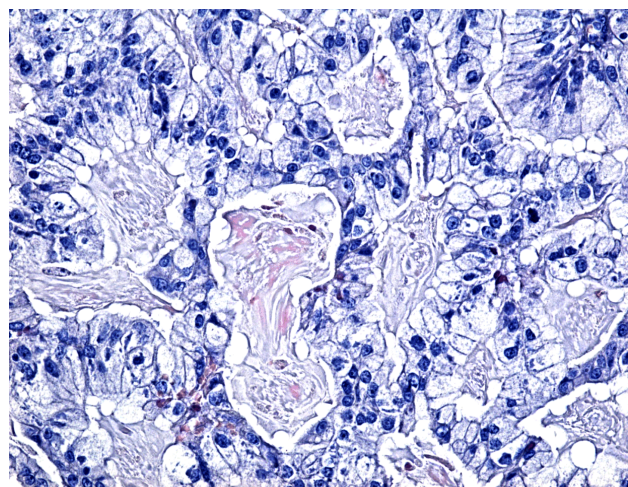
**Figure 1** – Tumor cells with numerous atypia and weak intracytoplasmic positive PAS-reaction. PAS–Hematoxylin staining,  $\times 200$ .



**Figure 2** – Tumor with papillary type proliferation, with fine stromal strains and vascular congestion. HE staining  $\times 100$ .

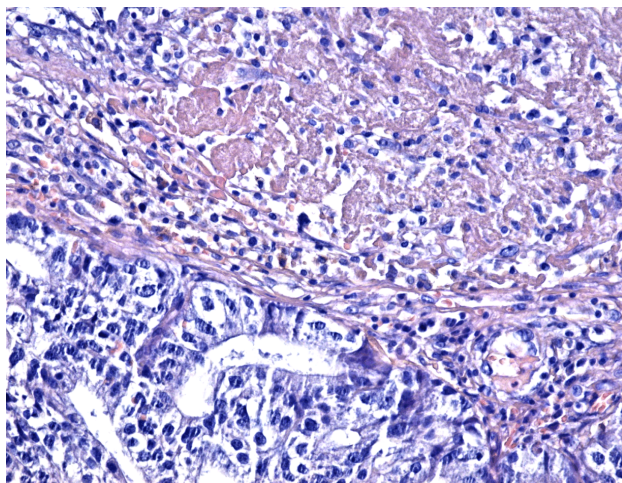


**Figure 3** – Polymorphic (cubic, cylindrical, polyhedral) tumor cells with moderate and severe nuclear atypia. HE staining,  $\times 200$ .

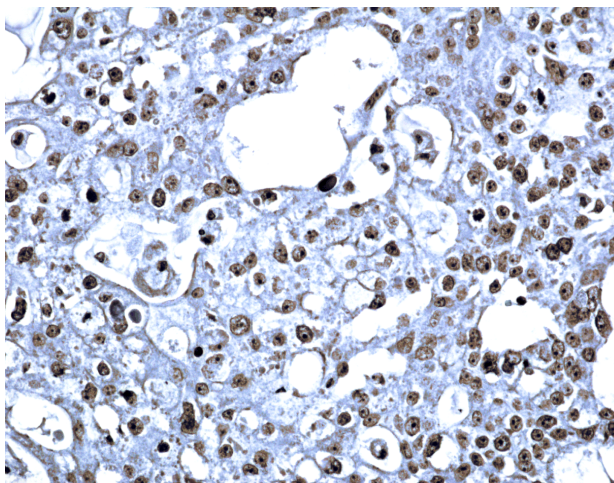


**Figure 4** – Tumoral glands with luminal secretion; cells with parakeratosis and slight focal dysplasia – mitotic figures. HE staining,  $\times 400$ .

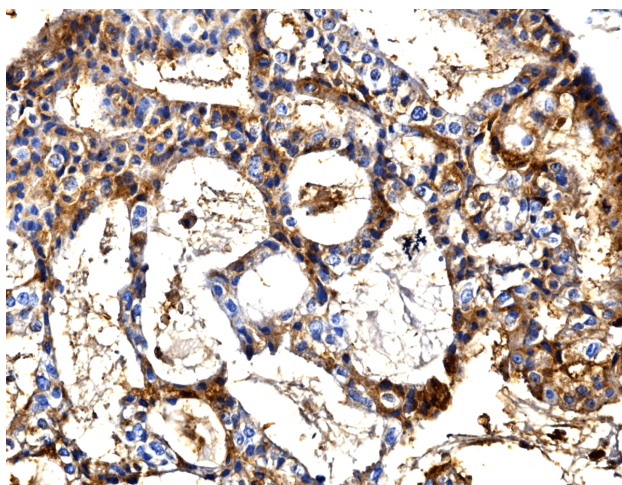




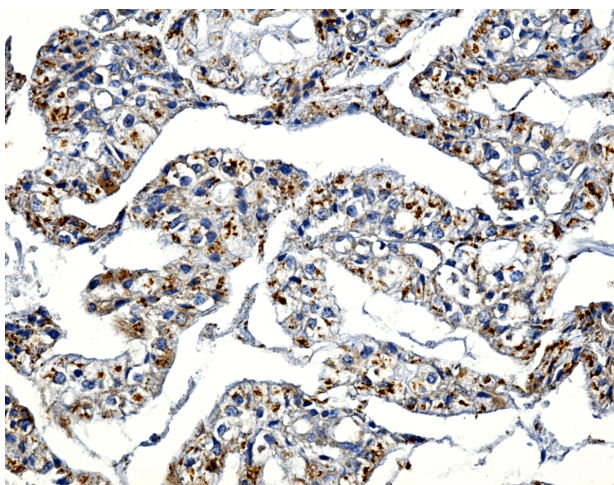
**Figure 5 – Tumoral area with necrosis and old hemorrhage (macrophages with hemosiderin). HE staining,  $\times 200$ .**



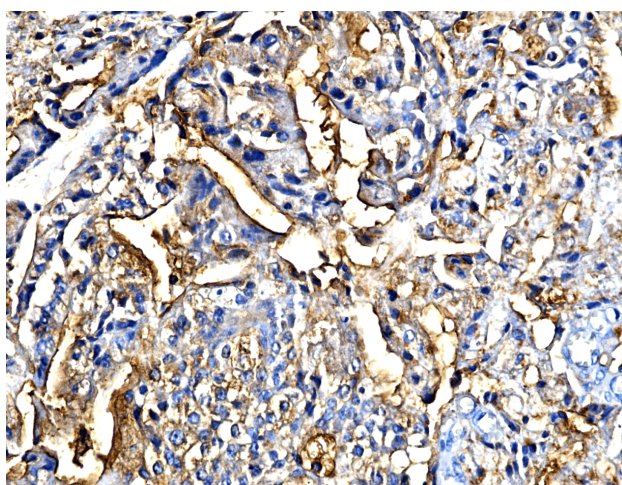
**Figure 6 – Tumor cells with a strong positive reaction to Bcl-2. Anti-Bcl-2 antibody immunomarking,  $\times 200$ .**



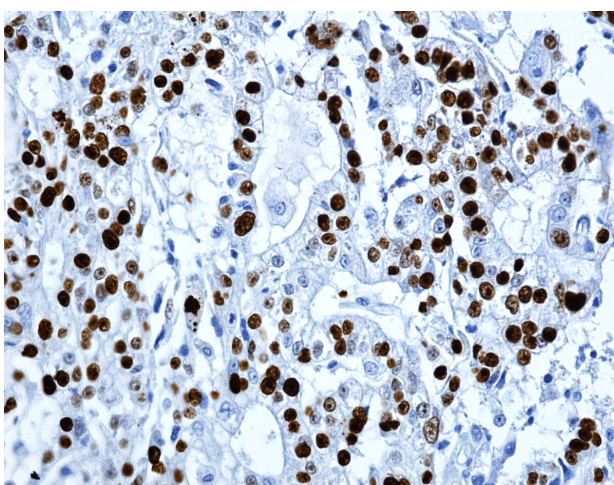
**Figure 7 – Very intense reaction of tumor cells to CEA antibody. Anti-CEA antibody immunomarking,  $\times 200$ .**



**Figure 8 – Tumor cells with diffuse reaction to cyclin 1. Anti-cyclin 1 antibody immunomarking,  $\times 200$ .**

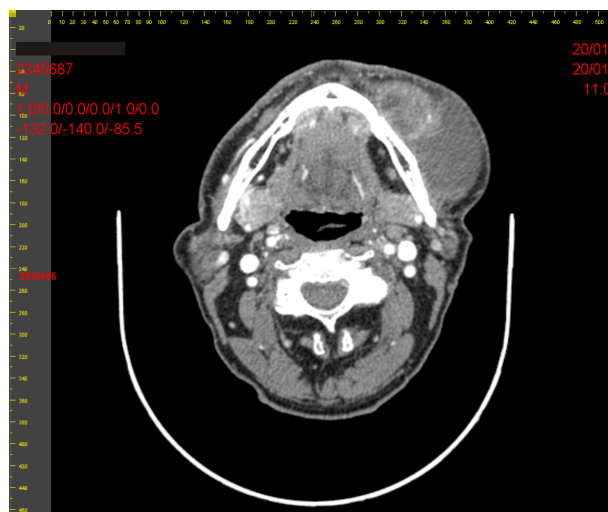


**Figure 9 – Tumoral parenchyma with intense reaction to EMA. Anti-EMA antibody immunomarking,  $\times 200$ .**



**Figure 10 – Tumor cells with intense proliferative activity (Ki67 positive in over 65% of the tumoral cells). Anti-Ki67 antibody immunomarking,  $\times 200$ .**





**Figure 11 – CT image of the tumor: a voluminous tumor with irregular edges, with a non-homogeneous structure, located in the left cheek.**

The risk factors in developing the ACC consist of radiation and genetic predisposition. The chronic alcohol consumption is not present in the ACC etiology, this being considered a risk factor for the Warthin's tumor.

The ACC is most frequently localized in the parotid gland, rarely in the minor salivary glands, especially the ones on the palate [5], and in less than 1% of the cases in the sublingual glands. In the head and neck region, there have been reported cases of ACC in the minor salivary glands [9], oral cavity [10], lips [11], palate [12], larynx [13], mandible [14], nose, paranasal sinuses [15]. Other locations of ACC in the human body could include the pancreas, stomach, prostate, breasts, lungs [16, 17]. The left cheek location of the tumor formation, with origin in the minor salivary glands from the oral cavity in the examined patient is a rare location for this type of cancer.

ACC is a malignant tumor of the salivary glands of low aggression [1, 18]; although, relapses and metastasis have been quoted in the literature, the secondary tumor recurring in 82% of the cases within five years from being diagnosed [19]. The relapse rate for this tumor varies between 30–50% [2], the rate of cervical metastasis between 3.8–16% [1, 19], the rate of distant metastasis between 7–29% [20], and the death rate varies between 1.3–26% [1, 19, 21]. Five-year survival rate is estimated at 91% of the cases and 10-year survival rate at 88% of the cases [1]. The age of the patient, the aspect and the histological grade of the tumor and the presence of the metastatic disseminations are considered prognosis factors for the tumor [22–26]. Reserved prognosis factors are: short term of the symptoms, incomplete excision, and mitosis frequency, the presence of focal necrosis, neural invasion, pleomorphism, infiltration and hyalinization of the stroma [22, 27]. The old age of this patient is considered the main factor for such quick relapse, one year from the initial surgical intervention and possibly also the comorbidities.

It is usually difficult to establish the ACC diagnosis. The ultrasound examination, X-ray and CT examination are usually used in the management plan of the tumor. The ultrasound, which is a non-invasive method used on a large scale, it is used to establish the dimensions of the

tumor, the location and nature of the tumor, as well as guiding the puncture biopsy. The CT examination is useful in establishing the dimensions of the tumor, the extension of the tumor, and its relations to the facial nerve and other head and neck structures, and the existence of metastasis [28].

In this case, the CT investigations provided information in regards to the dimensions, location and extension of the tumor, as well as the absence of metastasis, aspects which did not justified the quick relapse of the tumor formation.

The diagnosis was confirmed histopathologically. According to the literature, the salivary gland tumors can have their origins in the epithelial cells or myoepithelial cells, which can show signs of metaplasia (squamous, cartilaginous, oncocytoma, sebaceous, etc.). For this reason, it is difficult to classify this tumors and it is very important to determine their benign or malignant character.

ACC is a tumor frequently located in the parotid gland, rarely in the minor salivary glands. Macroscopic, ACC looks like an encapsulated tumor, of firm or moderate consistency that can be solid or cystic. Usually, the tumor is less than 3 cm in diameter. The presented patient had a tumor with dimensions of 48/88 mm, with cystic or cystic with seromucous content.

Microscopic, ACC is a tumor with multidirectional differentiation (acinar cells, cysts, myoepithelial cells), with various dispositions (patterns): solid, micro-cystic, papillary, follicular, with or without hemorrhage. The tumor cells contain “zymogen granules”, which are positive in the PAS staining and negative in the mucicarmine staining. The mitotic figures are generally scarce.

The salivary gland is made of acinar epithelial/ductal cells and/or myoepithelial basal cells. The monophasic tumors are made of only one type of cells (acinar/ductal or myoepithelial/basal cells), while the biphasic tumors include both types of cells. The IHC examination helps in cellular differentiation.

IHC, tumor cells are positive for cytokeratin (CK), transferrin, alpha-1-antitrypsin. CEA positivity suggests the differentiation of ductal epithelium. Also, the tumor expresses positivity for Ki67, p53, epidermal growth factor receptor (EGFR), etc.

Abrams *et al.* publishes a study conducted on 77 cases, in 1965, and proposes a five subtypes classification, with the following patterns: solid, micro-cystic, papillary-cystic, follicular and adenomatous [29].

ACC is generally a well-differentiated tumor, histologically represented by serous acinar cells rich in zymogen granules, intercalated with ductal-like cells, vacuolar cells, cells with clear cytoplasm with the above-mentioned patterns.

Low-grade histology is present in this case in the predominant cystic/papillary aspect, also called “organoid”. High grade involves anaplastic cellular aspect, abundant cytoplasm, nuclear pleomorphism, loss of acinar arrangement, vascular and perineural invasion, intra-tumor necrosis (with unfavorable prognosis).

Differential diagnosis is necessary in certain morphological forms of ACC with mucoepidermoid carcinomas, thyroid follicular carcinoma, etc.

The prognosis is unfavorable in some forms of dedifferentiated ACC, those with Ki67 over 5%.



Tumor relapses and rare metastasis of ACC in the minor salivary glands are quoted in literature. In this case, the tumor relapsed in less than one year.

## ✉ Conclusions

ACC is a rare tumor of the salivary glands, frequently affecting the parotid and very rarely the minor salivary glands. The slow clinical evolution explains the late arrival of the patient to the specialist. The confirmation of the diagnosis implies the correlation of the clinical examinations with the CT and histopathological examination. The regular staining with HE and PAS establish the ACC diagnosis. IHC, cellular proliferation factors analysis are elements of tumor prognosis. Unfavorable prognosis factors are: pain and/or the tumor adhesion to the neighboring tissues, cellular anaplasia or dedifferentiation, atypical multiple mitosis, necrosis, vascular and perineural invasion, the size of the tumor, incomplete resection determined by unfavorable anatomical relations, etc. The atypical evolution of the presented case could be due to multiple factors: late diagnosis (tumor was already large), comorbidities (chronic alcohol consumption), advanced age, and histological grading confirmed by the tumor proliferative index.

## Conflict of interests

The authors declare that they have no conflict of interests.

## References

- [1] Hoffman HT, Karnell LH, Robinson RA, Pinkston JA, Menck HR. National Cancer Data Base report on cancer of the head and neck: acinic cell carcinoma. *Head Neck*, 1999, 21(4):297–309.
- [2] Laskawi R, Rödel R, Zirk A, Arglebe C. Retrospective analysis of 35 patients with acinic cell carcinoma of the parotid gland. *J Oral Maxillofac Surg*, 1998, 56(4):440–443.
- [3] Luukkaa H, Kleim P, Leivo I, Koivunen P, Laranne J, Mäkitie A, Virtaniemi J, Hinkka S, Grénman R. Salivary gland cancer in Finland 1991–96: an evaluation of 237 cases. *Acta Otolaryngol*, 2005, 125(2):207–214.
- [4] Ellis GL, Auclair PL. Tumors of the salivary glands. In: \*\*\*. *Atlas of Tumor Pathology*. 3<sup>rd</sup> edition, Armed Forces Institute of Pathology (AFIP), Washington, D.C., 1996, 80–94.
- [5] Federspil PA, Constantinidis J, Karapantzios I, Pahl S, Markmann HU, Iro H. [Acinic cell carcinomas of the parotid gland. A retrospective analysis]. *HNO*, 2001, 49(10):825–830.
- [6] Stewart AK, Bland KI, McGinnis LS Jr, Morrow M, Eyre HJ. Clinical highlights from the National Cancer Data Base, 2000. *CA Cancer J Clin*, 2000, 50(3):171–183.
- [7] Al-Zaher N, Obeid A, Al-Salam ST, Al-Kayyali BS. Acinic cell carcinoma of the salivary glands: a literature review. *Hematol Oncol Stem Cell Ther*, 2009, 2(1):259–264.
- [8] Barnes L, Eveson JW, Reichart P, Sidransky D (eds). *Pathology and genetics of head and neck tumours*. World Health Organisation (WHO) Classification of Tumours, International Agency for Research on Cancer (IARC) Press, Lyon, 2005, 212–218.
- [9] Chou C, Zhu G, Luo M, Xue G. Carcinoma of the minor salivary glands: results of surgery and combined therapy. *J Oral Maxillofac Surg*, 1996, 54(4):448–453.
- [10] Keane WM, Denneny JC 3rd, Atkins JP Jr, McBrearty F. Acinic cell carcinoma of the oral cavity. *Otolaryngol Head Neck Surg*, 1982, 90(6):696–699.
- [11] Mocan S, Stolnicu S, Rădulescu D, Petrovan C. [Acinic cell adenocarcinoma of the lip]. *Rev Med Chir Soc Med Nat Iasi*, 2005, 109(1):164–169.
- [12] Utsunomiya T, Yamamoto H, Kuyama K, Itami M, Asanuma K. Acinic cell carcinoma of the palate: case report and immunohistochemical observation. *Arch Otolaryngol Head Neck Surg*, 1999, 125(9):1025–1028.
- [13] Boscolo-Rizzo P, da Mosto MC, Marchiori C, Boccato P. Transglottic acinic cell carcinoma. Case report and literature review. *ORL J Otorhinolaryngol Relat Spec*, 2004, 66(5):286–289.
- [14] Hara I, Ozeki S, Okamura K, Toshitani K, Taniguchi K, Honda T, Ohishi M. Central acinic cell carcinoma of the mandible. Case report. *J Craniomaxillofac Surg*, 2003, 31(6):378–382.
- [15] von Biberstein SE, Spiro JD, Mancoll W. Acinic cell carcinoma of the nasal cavity. *Otolaryngol Head Neck Surg*, 1999, 120(5):759–762.
- [16] Coyne JD, Dervan PA. Primary acinic cell carcinoma of the breast. *J Clin Pathol*, 2002, 55(7):545–547.
- [17] Kuopio T, Ekfors TO, Nikkanen V, Nevalainen TJ. Acinar cell carcinoma of the pancreas. Report of three cases. *APIMS*, 1995, 103(1):69–78.
- [18] Hickman RE, Cawson RA, Duffy SW. The prognosis of specific types of salivary gland tumors. *Cancer*, 1984, 54(8):1620–1624.
- [19] Vidyadhara S, Shetty AP, Rajasekaran S. Widespread metastases from acinic cell carcinoma of parotid gland. *Singapore Med J*, 2007, 48(1):e13–e15.
- [20] Lewis JE, Olsen KD, Weiland LH. Acinic cell carcinoma: clinicopathologic review. *Cancer*, 1991, 67(1):172–179.
- [21] Spiro RH, Huvos AG, Strong EW. Acinic cell carcinoma of salivary origin. A clinicopathologic study of 67 cases. *Cancer*, 1978, 41(3):924–935.
- [22] Miki H, Masuda E, Ohata S, Komaki K, Hirokawa M, Uehara H, Asano H, Monden Y. Late recurrence of acinic cell carcinoma of the parotid gland. *J Med Invest*, 1999, 46(3–4):213–216.
- [23] Mogoantă SŞ, Costache A, Muşiu G, Bungău SG, Ghiluşi M, Grosu F, Vasile M, Vilcea ID, Gherghinescu MC, Mogoantă L, Ion DA. A nonfunctional neuroendocrine tumor of the pancreas – a case report. *Rom J Morphol Embryol*, 2015, 56(2):511–519.
- [24] Pallag A, Roşca E, Țiţ D, Muşiu G, Bungău SG, Pop OL. Monitoring the effects of treatment in colon cancer cells using immunohistochemical and histoenzymatic technique. *Rom J Morphol Embryol*, 2015, 56(3):1103–1109.
- [25] Stoicescu M, Csepento C, Muşiu G, Bungău S. The role of increased plasmatic renin level in the pathogenesis of arterial hypertension in young adults. *Rom J Morphol Embryol*, 2011, 52(1 Suppl):419–423.
- [26] Totolici BD, Neamţu C, Bodog FD, Bungău SG, Goldiş DS, Matei M, Andercou AO, Amza OL, Gyori Z, Coldea L. Hemobilia by idiopathic aneurysm of cystic artery, fistulized in the biliary ways – clinical case. *Rom J Morphol Embryol*, 2017, 58(1):267–270.
- [27] Timon CI, Dardick I, Panzarella T, Thomas J, Ellis G, Gullane P. Clinico-pathological predictors of recurrence for acinic cell carcinoma. *Clin Otolaryngol Allied Sci*, 1995, 20(5):396–405.
- [28] Sakai O, Nakashima N, Takata Y, Furuse M. Acinic cell carcinoma of the parotid gland: CT and MRI. *Neuroradiology*, 1996, 38(7):675–679.
- [29] Abrams AM, Cornyn J, Scofield HH, Hansen LS. Acinic cell adenocarcinoma of the major salivary glands. A clinicopathologic study of 77 cases. *Cancer*, 1965, 18(9):1145–1162.

## Corresponding author

Camelia Liana Buhaş, Assistant Professor, MD, PhD, Department of Morphological Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, 1 Universităţii Street, 410087 Oradea, Romania; Phone +40745–647 201, e-mail: cameliabuhas@yahoo.com