ORIGINAL PAPER

RJME
Romanian Journal of Morphology & Embryology
http://www.rjme.ro/

Acinic cell carcinoma of the salivary glands: a retrospective clinicopathologic study of 12 cases

MARIA CRISTINA MUNTEANU[1)], CL. MĂRGĂRITESCU[2)], LUCIA CIONCA[3)], N. C. NIŢULESCU[1)], LUMINIŢA DĂGUCI[4)], E. M. CIUCĂ[1)]

[1)]*Department of Oral and Maxillofacial Surgery*
[2)]*Department of Pathology*
University of Medicine and Pharmacy of Craiova
[3)]*Department of Pathology,*
"Prof. Dr. Dan Theodorescu" Dental University Hospital, Bucharest
[4)]*Department of Prosthetics,*
University of Medicine and Pharmacy of Craiova

Abstract

Acinic cell carcinoma (ACC) is the third most common epithelial malignancy of the salivary glands in adults, with a low-grade malignancy that mainly occurs in the parotid gland and at a relatively younger age than other salivary gland tumors. We made a retrospective study on our acinic cell carcinoma casuistry aiming their clinico-pathological characterization and comparison with literature data. From 2000 through 2011 in our hospital were diagnosed only 12 cases of ACC. The clinico-epidemiological study revealed prevalence of these tumors in women, in the fourth decade of life and especially occurring in the parotid gland. The most common morphologic pattern of these tumors was a mixture of two or more variants with the solid/lobular and microcystic patterns more frequent associated. In 75% of investigated cases, the pTNM stage was I/II, with no cases of perineural or vascular invasion, but with lymph node dissemination presented in only three cases. Summing all these clinicopathological features, we conclude that for our casuistry the biological behavior of these tumors has been of low-grade malignancy.

***Keywords*:** acinic cell carcinoma, salivary gland, histological pattern.

Introduction

Acinic cell carcinoma (ACC) is a rare malignant epithelial tumor that accounts for about 1–6% of all salivary gland neoplasms [1]. It is a low-grade malignancy that occurs most often in the parotid gland with a predilection for females and presents at a relatively younger age than other salivary gland tumors [2]. Despite of low malignant behavior, ACC has a tendency to recur, to produce metastases (cervical lymph nodes and lungs), and may have an aggressive evolution with death rates ranging from 1.3% to 26% [3–5].

Regarding its histogenesis, most authors consider that ACC arise from neoplastic transformation of the terminal duct cells (intercalated duct cells) or from normal serous acinar cells [2, 6, 7]. As possible causes of ACC were incriminated previous radiation exposures [8] and familial predisposition [9] or perhaps like breast carcinoma it is a hormonally dependent tumor [2, 10].

The objective of this study was to report our experience in diagnosis of this tumor and to evaluate the major clinicopathological factors that might be involved in the prognosis of these patients.

Materials and Methods

We reviewed medical records from the Pathology Laboratory of Emergency County Hospital of Craiova and identified those patients who had been operated for salivary ACC from 2000 through 2011.

As clinical data, we noted each patient's sex, age and the site of the tumor and as pathological parameters, we look for histological patterns, involvement at the surgical margins, presence of perineural and/or vascular invasion and pTNM (Table 1).

Table 1 – ***Major clinicopathological features of the investigated ACC***

Case No.	Age [years]	Gender	Site	Histologic pattern	Surgical margins	Perineural invasion	Vascular invasion	pTNM
1.	43	F	Parotid	Solid	-	-	-	I (T1N0M0)
2.	47	F	Parotid	Solid	-	-	-	II (T2N0M0)
3.	52	F	Parotid	Microcystic	-	-	-	II (T2N0M0)

Case No.	Age [years]	Gender	Site	Histologic pattern	Surgical margins	Perineural invasion	Vascular invasion	pTNM
4.	32	M	Parotid	Papillary cystic	+	-	-	I (T1N0M0)
5.	55	F	Parotid	Mixed with more than two patterns	-	-	-	II (T2N0M0)
6.	44	F	Parotid	Solid	-	-	-	III (T2N1M0)
7.	49	M	Buccal mucosa	Mixed: solid + microcystic	-	-	-	I (T1N0M0)
8.	54	M	Upper lip	Mixed: solid + microcystic	-	-	-	I (T1N0M0)
9.	28	F	Parotid	Papillary cystic	-	-	-	II (T2N0M0)
10.	59	M	Parotid	Solid	-	-	-	III (T2N1M0)
11.	63	M	Parotid	Mixed with more than two patterns	-	-	-	II (T2N0M0)
12.	51	F	Parotid	Mixed with more than two patterns	+	-	-	IV (T2N2M0)

Paraffin blocks from these patients were process by classical histological techniques (HE stain) and for more detailed histopathological investigation were stained with Masson's trichrome kit (BioOptica, Albedo, Romania, code 21–010802IC) and PAS stain after diastase digestion (PAS-D) using alpha-amylase from porcine pancreas (Sigma-Aldrich, Albedo, Romania, code A3176) according to the producers' protocols. To illustrate more properly the acinar differentiation, we made an immunohistochemical detection for human amylase (G-10, mouse anti-human, monoclonal, Santa Cruz, Redox, Romania, code sc–46657) without antigen unmasking and incubating the slides overnight at 4^0C with the primary antibody diluted as 1:2000. The reactions were amplified with LSAB2 (Dako, Redox, Romania, code K0675) and visualized with 3,3'-diaminobenzidine (DAB) (Dako, Redox, Romania, code K3468). For counterstaining, we used Mayer's Hematoxylin. The resection margins that include normal salivary gland parenchyma were used as internal control.

The histopathological criteria for ACC diagnosis were those established by *WHO* (2005) and the images were acquired by utilizing a Nikon Eclipse 55i microscope (Nikon, Apidrag, Bucharest) equipped with a 5-megapixel cooled CCD camera and the Image ProPlus AMS7 software (Media Cybernetics Inc., Buckinghamshire, UK).

Results

Clinico-epidemiological data

According to the data presented in Table 1, the majority of ACCs developed in the fifth decade of life (five cases, respective 41.66%), with an average of 45.75 years. The youngest patient had 28-year-old and the oldest was 63 years. Women were affected more frequently than men in a ratio of 1.4 to 1, with no age predilection.

Almost 84% of all ACCs occurred in the parotid gland, and only in two cases, the tumors involved the intraoral minor salivary glands, respective the right buccal and the upper lip mucosa groups. No correlation could be established between lesional topography and age or sex.

Histopathological aspects

The most frequently encountered histological pattern was the solid form present in all investigated cases, but extensively in only four cases (33.33%) (Figure 1, A and B). In this neoplastic growth pattern, tumor cells are closely apposed to each another but with a heterogeneous cellular composition, in some areas prevailing the acinar cell type, while in other areas the nonspecific glandular cells or even clear cells predominated.

In almost 42% of the cases, we noticed a mixture of two or more growth patterns with the solid/lobular and microcystic patterns more frequently associated (Figure 1C).

In the microcystic pattern, there are numerous small spaces within solid neoplastic proliferations usually outlined by acinar type cell and rarely by vacuolated and intercalated duct type cells (Figure 1D).

This growth pattern was predominant only in one case. In other two cases, the prevalent pattern was the papillary-cystic form consisting in prominent cystic spaces, partially filled with papillary growths lined by intercalated duct-type cells, vacuolated cells and acinary differentiated cells (Figure 1E).

In one of the mixed growth pattern, we noticed association of a follicular pattern, characterized by multiple cystic lumens filled with eosinophilic proteinaceous material that reproduce a thyroid follicle-like appearance (Figure 1F).

Cytologically, the acinar cell differentiation is the most characteristic cell type without being the prevailing one. Typically, neoplastic acinar cells are usually polygonal, have abundant, pale basophilic cytoplasm with purplish cytoplasmic granules and eccentrically located, round, dark, basophilic nuclei (Figure 2A).

These cells can be arranged in organoid fashion, in sheets or as randomly scattered foci. They are easily recognized with PAS-D stain, which highlights the cytoplasmic secretory, zymogen-like granules (Figure 2, B and C).

In the majority of the investigated cases, immunohistochemistry for amylase identified the neoplastic cells with acinar differentiation. The reactivity was exclusively cytoplasmic and corresponded to the location of zymogen-like granules (Figure 2, D and E).

Other encountered cell types were:

▪ intercalated duct-like cells that surround variably sized luminal spaces consisting in smaller, cuboidal cells with eosinophilic to amphophilic cytoplasm and central nuclei, that ranged from deeply basophilic to vesicular chromatin pattern (Figure 2F);

▪ non-specific glandular cells typically arranged in syncytial sheets that were round to polygonal, with amphophilic to eosinophilic cytoplasm and round, basophilic to vesicular nuclei (Figure 2, G–I);

▪ vacuolated cells characterized by vacuoles that filled most of the cytoplasmic, being clear under HE stain and unreactive with PAS stain (Figure 2, J–L).

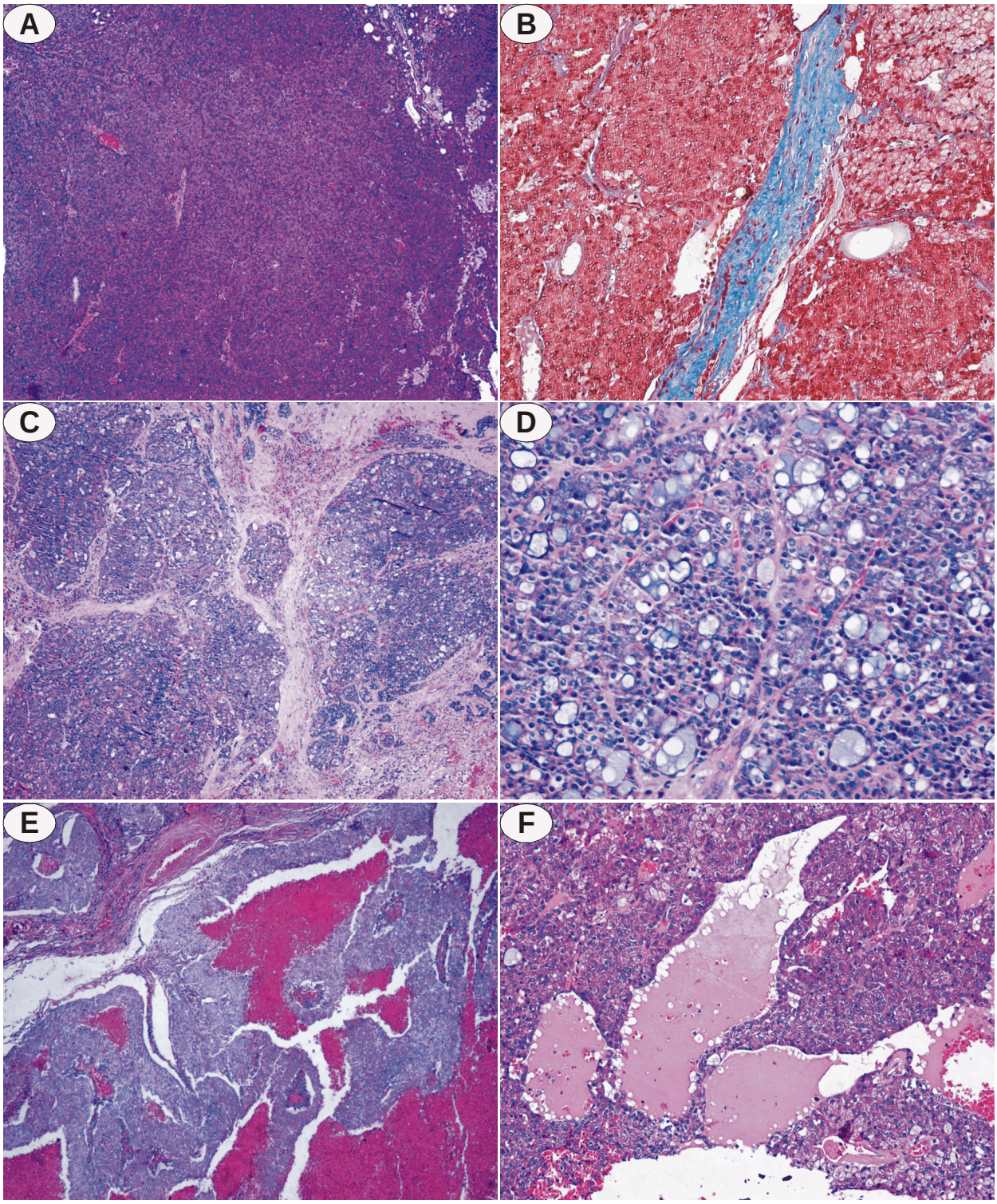

Figure 1 – ***ACC, histologic growth patterns: (A) and (B) Solid pattern (HE stain/Masson's trichromic stain, ×40/×100); (C) Mixed patter – a mixture of solid and microcystic patterns (HE stain, ×40); (D) Microcystic pattern (HE stain, ×40); (E) Papillary-cystic pattern (HE stain, ×40); (F) Follicular pattern (HE stain, ×100).***

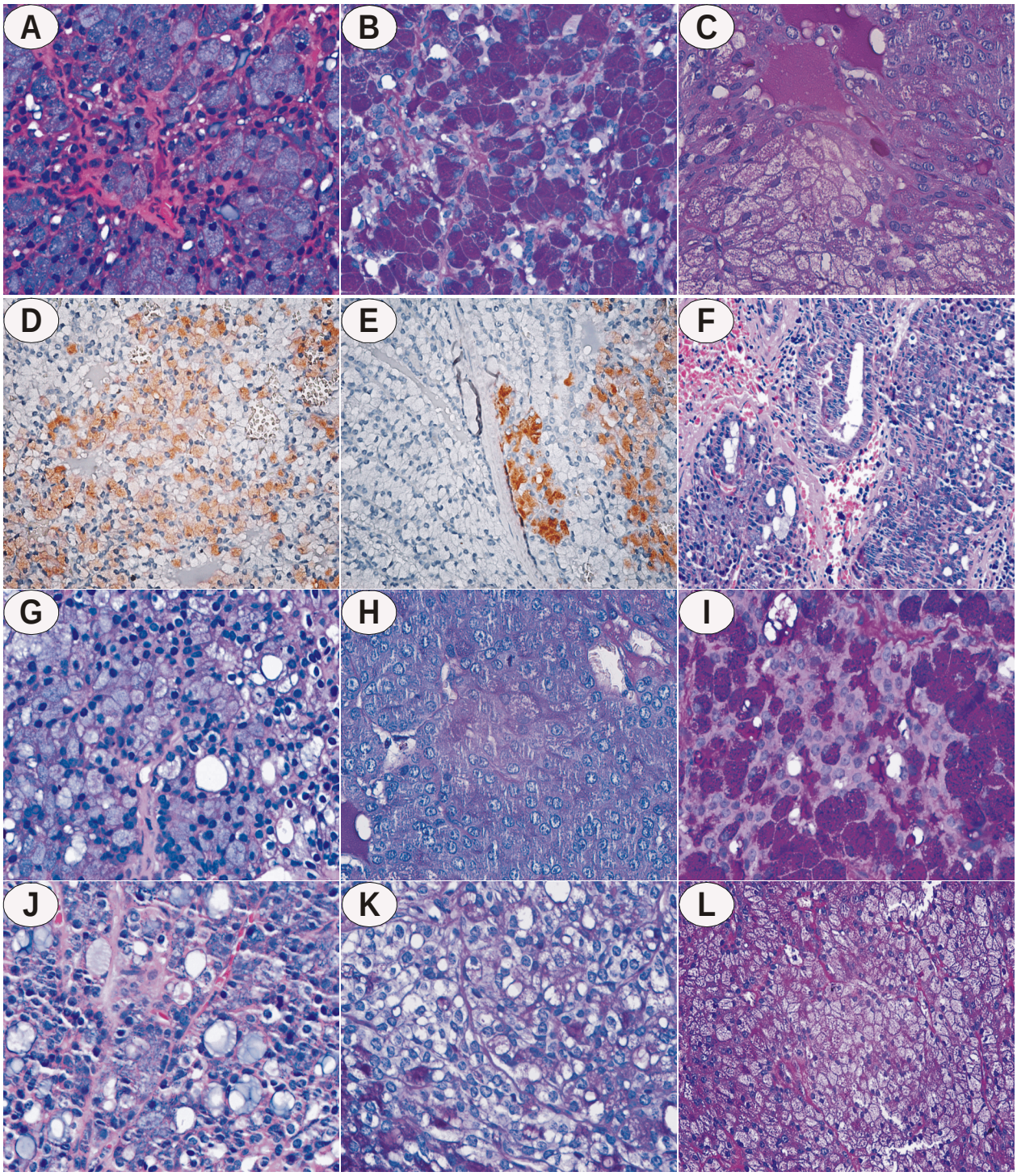

Figure 2 – ***ACC, cytologic differentiations: (A) Acinar cells (HE stain, ×400); (B) Acinar cells – distinctly granular cytoplasm (PAS-D stain, ×400); (C) Acinar cells – finely reticular cytoplasm (HE stain, ×400); (D) and (E) Acinar cells, amylase positive (brown), ×200; (F) Intercalated duct-like cells (HE stain, ×200); (G) Non-specific glandular cells-round to polygonal with amphophilic to eosinophilic cytoplasm (HE stain, ×400); (H) and (I) Non-specific glandular cells-without zymogen-like granules in cytoplasm mixed with typical acinar cells (PAS-D stain, ×400); (J) Vacuolated cells (HE stain, ×400); (K) Vacuolated cells (PAS-D stain, ×400); (L) Vacuolated and clear cells (PAS-D stain, ×200).***

In four cases the tumor dimensions was less than 2 cm (T1) and they were well circumscribed, but in the other cases tumors infiltrated adjacent normal tissues (Figure 3, A and B). The stroma varied from delicate fibrovascular tissue to extensively collagenous tissue (Figure 3, C and D). In two cases, we noticed a prominent lymphoid infiltrate of the stroma, including the presence of germinal centers (Figure 3E). Hemorrhages and hemosiderin deposits are constant aspects in the connective tissue of these tumors, and where thus present also in our pathology palette (Figure 3F). There were no cases of perineural or vascular invasion, but lymph node dissemination was noticed in three cases.

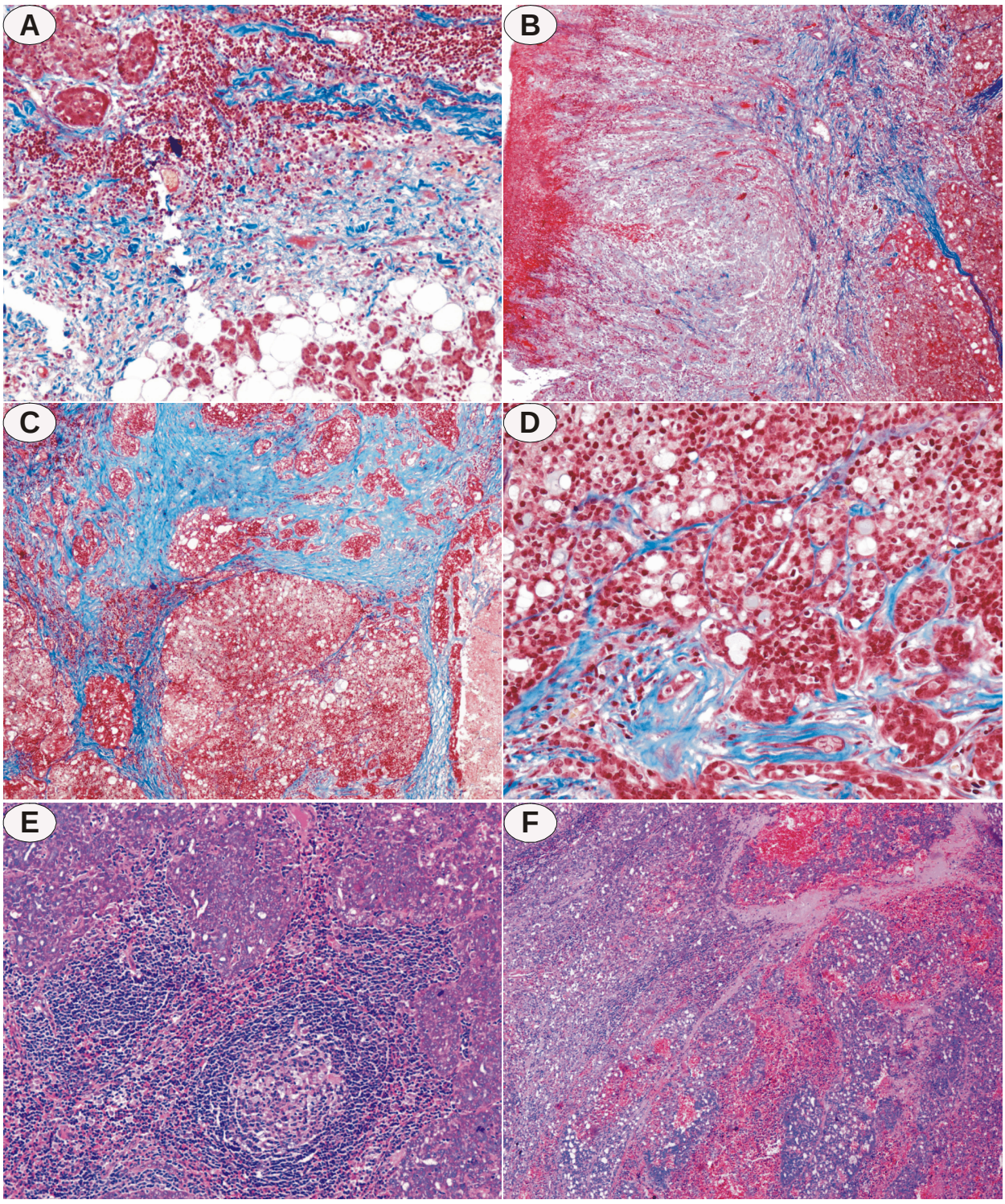

Figure 3 – ***ACC, stromal features: (A) Invasion of the adjacent normal parotid gland (Masson's trichromic stain, ×40); (B) Invasion of the adjacent normal oral mucosa (Masson trichromic stain, ×40); (C) and (D) From delicate fibrovascular tissue to extensively collagenous tissue (Masson trichromic stain, ×40/×200); (E) A prominent lymphoid infiltrated stroma with follicular and germinal center formation (HE stain, ×40); (F) Hemorrhage infiltration of stroma (HE stain, ×40).***

Discussion

The first cases of ACC were reported back in 1892, by Nasse D [11]. Before the *WHO*'s revised classification of salivary gland tumors of 1991 [12], many authors used the term "acinic cell tumor" for these neoplasms questioning thus their malignant behavior. The malignant potential of this entity was first noted by Buxton RW *et al.* [13] and Foote FW Jr and Frazell EL [14], as they have classified it as acinic cell adenocarcinoma.

Our findings showed an average of 45.75 years for the incidence of ACC and women to man ratio of 1.4 to 1. The literature data showed a prevalence for ACC between the ages of 40 and 49 years [15–20], affecting twice as many females as males [15, 16, 18, 19]. Although the youngest patient in our series was 28-year-

old, the vast majority of authors presented that ACC can develop at any age, and accounting for 6–37% of total parotid malignancies in children [21–25].

Consistent with our results, this type of salivary tumor develops especially in the parotid gland, almost 80% of ACC occurring at this level. The second location of ACC is the intraoral minor salivary glands (17%), followed by submandibular glands (4%) and sublingual glands (less than 1%) [1, 2, 26, 27]. ACC seems to be one of the most frequent salivary gland malignancies that occur bilaterally, up to 3% of tumors being bilateral, usually in the parotid glands [28].

Over time, various authors have used varied terms to describe the several histomorphologic patterns and cellular features of these tumors. Thus, Batsakis JG *et al.* [29, 30] have described for ACC seven different histologic patterns: acinar-lobular, microcystic, follicular, papillary cystic, medullary, ducto-glandular and primitive tubular, while Ellis GL and Corio RL [31] recognized only three categories: cystic papillary, follicular, and solid. However, descriptive categories (solid, microcystic, papillary-cystic and follicular) presented by Abrams AM *et al.* in 1965 [32] have been useful to pathologists over the last 30 years and are still applicable today [2]. We must keep in mind that these designations related to the tumor pattern do not define specific subtypes of ACC for clinical, therapeutic, or prognostic purposes.

Most studies indicate solid and microcystic patterns as the major histomorphologic patterns for ACC [3, 5, 17, 31]. Sometimes, a mixture of patterns is a common aspect as seen in our casuistry. In 42% of the cases, we noticed a mixture of two or more growth patterns with the solid/lobular and microcystic patterns being more frequent associated. The second most frequently encountered growth pattern was the solid type (33.33%), followed by papillary-cystic (16.66%) and microcystic (8.33%). As we described in solid growth pattern, proliferate well-differentiated acinar cells with prominent basophilic to grey granularity of their cytoplasm intermingled with foci of non-specific glandular cells with eosinophilic or amphophilic cytoplasm [30]. In contrast to acinar differentiation of the solid variant, the microcystic growth pattern recapitulates the terminal (intercalated) duct acinar unit [33]. It consists of numerous small spaces outline by cuboidal cells with amphophilic or eosinophilic cytoplasm, with distinct borders, which exhibit a characteristic lattice-like [4] or fenestrated [15] appearance. The follicular type seems to be the least frequent one in both major and minor salivary gland cases [5, 16, 19, 34, 35]. It shows an exaggerated acinar microcystic pattern in which dilated acini are lined by flattened epithelium and contain colloid-like amorphous eosinophilic material [36]. Papillocystic pattern consists of cystic spaces filled by papillary projections outlined by diverse cell types such as: acinic cells, vacuolated cells, intercalated cells, non-specific glandular cells, and clear cells [30]. In dedifferentiated ACC, coexist areas of low-grade ACC with areas of dedifferentiated high-grade ACC or undifferentiated carcinoma [15, 37, 38, 39, 40]. Also, there have been reports of well differentiated ACCs with lymphoid stroma present, as well as circumscribed encapsulated tumors with a solid or microcystic pattern in which tumor cells are surrounded and intermingled with prominent lymphoid response [41]. Other histologic variants described in the literature for ACC were hybrid tumors [41, 42] and tumors with extensive neuro-endocrine differentiation [43].

Considering this variable histologic appearance coupled with its uncommon occurrence, this explains the diagnostic difficulties in cases presenting with this tumor. This fact becomes evident in tumors were acinar differentiation are less obvious and where special stains (PAS-D and anti-amylase antibodies) play a key role in their diagnosis. Follicular thyroid carcinoma typically resembles ACC, which can be differentiated by anti-thyroglobulin staining. The differential diagnosis for the papillary-cystic tumors includes cystadenocarcinoma (with mucocytes identified with mucicarmine stain) and mucoepidermoid carcinoma (with epidermoid cells, mucocytes that are strongly mucicarminophilic, and the absence of serous acinar cells). In minor salivary glands, polymorphous low-grade adenocarcinoma is also considered, but papillary-cystic pattern is not usually dominant in the latter, and there is a greater affinity for perineural growth, a more homogeneous cell population, and a greater tendency for single-file cell infiltration at the tumor's periphery than in acinic cell adenocarcinoma [1]. Occurrence of clear cells in ACC impose differential diagnosis with other clear cell neoplasms, such as mucoepidermoid carcinoma, epithelial-myoepithelial carcinoma, clear cell adeno-carcinoma, clear cell oncocytoma, and metastatic renal cell carcinoma (in which clear neoplastic cells are positive for glycogen stains).

Overall, it seems that the biologic behavior of ACC cannot be reliably predicted based on histomorphologic features [5, 19, 31, 32, 44]. Therefore, if Perzin KH and LiVolsi VA [4] and Colmenero C *et al.* [16] reported that patients with a solid growth pattern had a worse prognosis, Spiro RH *et al.* [3] noticed 100% mortality for patients with papillary-cystic pattern. It is generally accepted that dedifferentiated carcinomas are associated with a poor clinical outcome, as they tend to involve the whole parotid gland, invade the facial nerve, blood and lymphatic vessels, and metastasis in regional lymph nodes.

Attempts of histological grading have been controversial and inconsistent, because there has been little uniformity among investigators about the criteria for a grading system, and at least one of the grading schemes uses clinical staging criteria, such as size and site, as part of the grading criteria [15]. Staging is often a better predictor of outcome than the histologic grading. In general, features that are associated with more aggressive tumors include frequent mitoses, focal necrosis, neural invasion, pleomorphism, infiltration (not circumscribed), stromal hyalinization, incomplete resection, large size, submandibular gland and involvement of the deep lobe of the parotid gland [3, 4, 15, 31, 37, 42]. Our investigation found that almost 67% of diagnosed ACC had infiltration of adjacent normal tissues, lymph node dissemination in 25% of the patients, and no case of perineural or vascular invasion.

Despite being a low-grade neoplasm, death rates due to the tumor range from 1.3% to 26%, with local recurrence of 8.3–45%, regional lymph node involvement of 3.8–16%, and distant metastasis of 2.6–14% [3, 4, 5, 31, 32, 45]. The most frequent site of ACC metastasis includes: cervical lymph nodes, liver, lungs, contralateral orbit and bones (thoracic spine) [46–48].

Conclusions

In our experience, ACC developed especially in the fifth decade of life, more frequent in women, and with the parotid as the most frequently involved salivary gland. Histopathologically, the most common growth pattern was a mixture of two or more variants with the solid/lobular and microcystic patterns more frequent associated. About two thirds of the cases were diagnosed in stage I and II, while lymph node dissemination was noticed only in three cases confirming their low-grade malignancy.

References

[1] Ellis GL, Auclair PL, *Tumors of the salivary glands. Atlas of tumor pathology*, 3rd Series, Fascicle 17, Armed Forces Institute of Pathology, Washington, D.C., 1996, 183.

[2] Barnes L, Eveson JW, Reichart P, Sidransky D, *World Health Organization Classification of Tumours. Pathology and genetics of head and neck tumours*, IARC Press, Lyon, 2005, 216.

[3] Spiro RH, Huvos AG, Strong EW, *Acinic cell carcinoma of salivary origin. A clinicopathologic study of 67 cases*, Cancer, 1978, 41(3):924–935.

[4] Perzin KH, LiVolsi VA, *Acinic cell carcinomas arising in salivary glands: a clinicopathologic study*, Cancer, 1979, 44(4):1434–1457.

[5] Lewis JE, Olsen KD, Weiland LH, *Acinic cell carcinoma. Clinicopathologic review*, Cancer, 1991, 67(1):172–179.

[6] Dardick I, *Mounting evidence against current histogenetic concepts for salivary gland tumorigenesis*, Eur J Morphol, 1998, 36(Suppl):257–261.

[7] Dardick I, Burford-Mason AP, *Current status of histogenetic and morphogenetic concepts of salivary gland tumorigenesis*, Crit Rev Oral Biol Med, 1993, 4(5):639–677.

[8] 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.

[9] Kane WJ, McCaffrey TV, Olsen KD, Lewis JE, *Primary parotid malignancies. A clinical and pathologic review*, Arch Otolaryngol Head Neck Surg, 1991, 117(3):307–315.

[10] 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.

[11] Nasse D, *Die Geschwülste der Speicheldrüsen und verwandte Tumoren des Kopfes*, Arch Klin Chir, 1892, 44:233–302.

[12] Seifert G, Sobin LH, *Histological typing of salivary gland tumours*, World Health Organization International Histological Classification of Tumours, 2nd edition, Springer-Verlag, New York, 1991.

[13] Buxton RW, Maxwell JH, French AJ, *Surgical treatment of epithelial tumors of the parotid gland*, Surg Gynecol Obstet, 1953, 97(4):401–416.

[14] Foote FW Jr, Frazell EL, *Tumors of the major salivary glands*, Cancer, 1953, 6(6):1065–1133.

[15] Batsakis JG, Luna MA, el-Naggar AK, *Histopathologic grading of salivary gland neoplasms: II. Acinic cell carcinomas*, Ann Otol Rhinol Laryngol, 1990, 99(11):929–933.

[16] Colmenero C, Patron M, Sierra I, *Acinic cell carcinoma of the salivary glands. A review of 20 new cases*, J Craniomaxillofac Surg, 1991, 19(6):260–266.

[17] 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.

[18] Napier SS, Herron BT, Herron BM, *Acinic cell carcinoma in Northern Ireland: a 10-year review*, Br J Oral Maxillofac Surg, 1995, 33(3):145–148.

[19] Oliveira P, Fonseca I, Soares J, *Acinic cell carcinoma of the salivary glands. A long term follow-up study of 15 cases*, Eur J Surg Oncol, 1992, 18(1):7–15.

[20] Spafford PD, Mintz DR, Hay J, *Acinic cell carcinoma of the parotid gland: review and management*, J Otolaryngol, 1991, 20(4):262–266.

[21] Baker SR, Malone B, *Salivary gland malignancies in children*, Cancer, 1985, 55(8):1730–1736.

[22] Callender DL, Frankenthaler RA, Luna MA, Lee SS, Goepfert H, *Salivary gland neoplasms in children*, Arch Otolaryngol Head Neck Surg, 1992, 118(5):472–476.

[23] Kessler A, Handler SD, *Salivary gland neoplasms in children: a 10-year survey at the Children's Hospital of Philadelphia*, Int J Pediatr Otorhinolaryngol, 1994, 29(3):195–202.

[24] Orvidas LJ, Kasperbauer JL, Lewis JE, Olsen KD, Lesnick TG, *Pediatric parotid masses*, Arch Otolaryngol Head Neck Surg, 2000, 126(2):177–184.

[25] Rogers DA, Rao BN, Bowman L, Marina N, Fleming ID, Schropp KP, Lobe TE, *Primary malignancy of the salivary gland in children*, J Pediatr Surg, 1994, 29(1):44–47.

[26] Waldron CA, el-Mofty SK, Gnepp DR, *Tumors of the intraoral minor salivary glands: a demographic and histologic study of 426 cases*, Oral Surg Oral Med Oral Pathol, 1988, 66(3):323–333.

[27] Zbaeren P, Lehmann W, Widgren S, *Acinic cell carcinoma of minor salivary gland origin*, J Laryngol Otol, 1991, 105(9): 782–785.

[28] Gnepp DR, Schroeder W, Heffner D, *Synchronous tumors arising in a single major salivary gland*, Cancer, 1989, 63(6):1219–1224.

[29] Batsakis JG, *Tumors of the head and neck: clinical and pathological considerations*, 2nd edition, Williams & Wilkins, Baltimore, 1979, 39–44.

[30] Batsakis JG, Wozniak KJ, Regezi JA, *Acinous cell carcinoma: a histogenetic hypothesis*, J Oral Surg, 1977, 35(11):904–906.

[31] Ellis GL, Corio RL, *Acinic cell adenocarcinoma. A clinicopathologic analysis of 294 cases*, Cancer, 1983, 52(3):542–549.

[32] Abrams AM, Cornyn CJ, Scofield HH, Hansen LS, *Acinic cell adenocarcinoma of the major salivary glands. A clinicopathologic study of 77 cases*, Cancer, 1965, 18(9):1145–1162.

[33] Angeles-Angeles A, Caballero-Mendoza E, Tapia-Rangel B, Cortés-González R, Larriva-Sahd J, *Giant acinic cell parotid gland adenocarcinoma of the papillary-cystic type*, Rev Invest Clin, 1988, 50(3):245–248.

[34] Abrams AM, Melrose RJ, *Acinic cell tumors of minor salivary gland origin*, Oral Surg Oral Med Oral Pathol, 1978, 46(2): 220–233.

[35] Warner TF, Seo IS, Azen EA, Hafez GR, Zarling TA, *Immunocytochemistry of acinic cell carcinomas and mixed tumors of salivary glands*, Cancer, 1985, 56(9):2221–2227.

[36] Chaudhry AP, Cutler LS, Leifer C, Satchidanand S, Labay G, Yamane G, *Histogenesis of acinic cell carcinoma of the major and minor salivary glands. Aan ultrastructural study*, J Pathol, 1986, 148(4):307–320.

[37] el-Naggar AK, Batsakis JG, Luna MA, McLemore D, Byers RM, *DNA flow cytometry of acinic cell carcinomas of major salivary glands*, J Laryngol Otol, 1990, 104(5):410–416.

[38] Henley JD, Geary WA, Jackson CL, Wu CD, Gnepp DR, *Dedifferentiated acinic cell carcinoma of the parotid gland: a distinct rarely described entity*, Hum Pathol, 1997, 28(7): 869–873.

[39] Di Palma S, Corletto V, Lavarino C, Birindelli S, Pilotti S, *Unilateral aneuploid dedifferentiated acinic cell carcinoma associated with bilateral low-grade diploid acinic cell carcinoma of the parotid gland*, Virchows Arch, 1999, 434(4):361–365.

[40] Stanley RJ, Weiland LH, Olsen KD, Pearson BW, *Dedifferentiated acinic cell (acinous) carcinoma of the parotid gland*, Otolaryngol Head Neck Surg, 1988, 98(2):155–161.
[41] Ellis GL, Auclair PL, Gnepp DR, *Surgical pathology of salivary glands*, W. B. Saunders, Philadelphia, 1991, 299–317.
[42] Guimaraes DS, Amaral AP, Prado LF, Nascimento AG, *Acinic cell carcinoma of salivary glands: 16 cases with clinicopathologic correlation*, J Oral Pathol Med, 1989, 18(7):396–399.
[43] Roy S, Dhingra KK, Gupta P, Khurana N, Gupta B, Meher R, *Acinic cell carcinoma with extensive neuroendocrine differentiation: a diagnostic challenge*, Head Neck Pathol, 2009, 3(2):163–168.
[44] Hamper K, Caselitz J, Arps H, Askensten U, Auer G, Seifert G, *The relationship between nuclear DNA content in salivary gland tumors and prognosis. Comparison of mucoepidermoid tumors and acinic cell tumors*, Arch Otorhinolaryngol, 1989, 246(5):328–332.
[45] Batsakis JG, Chinn EK, Weimert TA, Work WP, Krause CJ, *Acinic cell carcinoma: a clinicopathologic study of thirty-five cases*, J Laryngol Otol, 1979, 93(4):325–340.
[46] Schwentner I, Obrist P, Thumfart W, Sprinzl G, *Distant metastasis of parotid gland tumors*, Acta Otolaryngol, 2006, 126(4):340–345.
[47] Tavora F, Rassaei N, Shilo K, Foss RD, Galvin JR, Travis WD, Franks TJ, *Occult primary parotid gland acinic cell adenocarcinoma presenting with extensive lung metastasis*, Arch Pathol Lab Med, 2007, 131(6):970–973.
[48] Vidyadhara S, Shetty AP, Rajasekaran S, *Widespread metastases from acinic cell carcinoma of parotid gland*, Singapore Med J, 2007, 48(1):e13–e15.

Corresponding author
Claudiu Mărgăritescu, Associate Professor, MD, PhD, Department of Pathology, Faculty of Dentistry, University of Medicine and Pharmacy of Craiova, 2–4 Petru Rareş Street, 200349 Craiova, Romania; Phone +40740–152 550, e-mail: c_margaritescu2000@yahoo.com

Received: February 28th, 2012

Accepted: May 25th, 2012