Int J Clin Exp Pathol 2014;7(11):8205-8210
www.ijcep.com /ISSN:1936-2625/IJCEP0002340

Case Report

Multifocal canalicular adenoma of the minor labial salivary glands

María Elena Samar[1], Rodolfo Esteban Avila[2], Ismael Bernardo Fonseca[2], William Anderson[3], Gabriel M Fonseca[1,4], Mario Cantín[4,5,6]

[1]Faculty of Dentistry, National University of Cordoba, Cordoba, Argentina; [2]Faculty of Medical Sciences, National University of Cordoba, Cordoba, Argentina; [3]Department of Pathology, New Cross Hospital, Wolverhampton, United Kingdom; [4]CIMA Research Group, Faculty of Dentistry, Universidad de La Frontera, Temuco, Chile; [5]Doctoral Program in Morphological Sciences, CEMyQ, Faculty of Medicine, Universidad de La Frontera, Temuco, Chile; [6]Center of Research in Biomedical Sciences, Universidad Autónoma de Chile, Temuco, Chile

Received September 5, 2014; Accepted October 31, 2014; Epub October 15, 2014; Published November 1, 2014

Abstract: Canalicular adenoma (CA) is an uncommon benign neoplasia of salivary glands which is clinically difficult to recognise. Despite having an excellent prognosis, the histological diagnosis and clinical management of this entity can be troublesome. While the main differential diagnosis to consider is basal cell adenoma (BCA), similar histological patterns and multifocality have been observed in adenoid cystic carcinoma (ACC) and polymorphous low-grade adenocarcinoma (PLGA), both locally-aggressive malignancies which require radically different treatment to CA. An emphasis has been placed on the value of immunohistochemistry in avoiding diagnostic and surgical errors. CA is positive for AE1/AE3, CD117 and S-100 protein, and negative for p63, α-SMA, Ki 67 and vimentin. Here we discuss the case of a 61-year-old female with CA in her right upper lip, showing multifocal growth histologically. The differential diagnosis with other adenomas is discussed in addition to the role of immunohistochemical studies that can confirm the clinical and surgical findings.

Keywords: Lip, minor salivary glands, benign neoplasia, canalicular adenoma

Introduction

Canalicular adenoma (CA) is a benign neoplasia of salivary glands, which although representing less than 1% of salivary gland tumours, is the second or third most common benign tumour of minor salivary glands [1, 2]. Historically considered a variant of basal cell adenoma (BCA), it wasn't until 1991 that the World Health Organisation (WHO) recognised this entity as being different to other salivary gland adenomas, due to its distinct clinical, morphological, and immunohistochemical characteristics [3-5]. After this the older term "monomorphic adenoma", used to differentiate this and other neoplasms from pleomorphic adenoma fell into disuse [6].

Peak incidence of CA is in the seventh decade and shows a female predominance (1.8:1) [5, 7]. It occurs almost exclusively in the oral cavity, principally involving the minor salivary glands in the mucosa of the upper lip in around 80% of cases [5]. Some authors have reported rare cases in the palate (10%), parotid, oesophagus, and mandible [3, 5, 8-10].

Clinically, CA usually presents as a well-demarcated, occasionally blue-tinged nodule measuring between 0.5-2 cm, which is otherwise asymptomatic. Prognosis is excellent, and recurrence is extremely rare even if just locally excised [5].

The histological appearance of CA is uniform, with cells distributed in solid structures, trabeculae, tubules, and cribriform or membranous patterns, therefore presenting a diagnostic challenge [7, 11]. There may be a fibrous capsule, and the presence of multiple adjacent foci is a relatively frequent finding microscopically [5]. Here we present an unusual case of CA affecting the right upper lip showing multifocal growth histologically, and review its differential diagnosis with other salivary gland tumours.

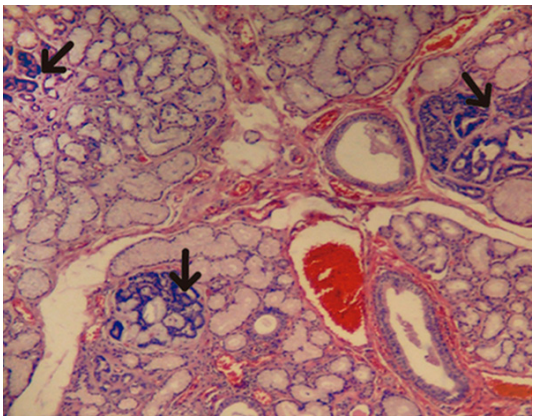

Figure 1. Multifocal canalicular adenoma of the upper lip. Multiple tumour nodules (arrows) located in glandular tissue. H/E. Original magnification ×40.

Case report

A 61-year-old female with a history of smoking presented with a 12-month history of a slow-growing nodule in the mucosa of her right upper lip. Examination of the oral cavity revealed a tender, solitary nodular lesion with a violaceous overlying mucosa without ulceration or bleeding. An informed consent was signed. Once the tumour was removed under local anaesthesia, macroscopic examination showed a brown, 2.3×1.6×1 cm lesion with an irregular surface. Areas of vascular congestion were seen on sectioning. The tissue was stained with haematoxylin and eosin (H & E), periodic acid Schiff (PAS), and toluidine blue at pH 3.8 and immunohistochemical studies were done with AE1/AE3, CD117, S-100 protein, vimentin, α-SMA, p63 and Ki 67.

Histopathological examination revealed a mucosal surface lined with stratified squamous epithelium. Deep to this were mixed labial salivary glands, predominantly mucous acini, which were partially surrounded by skeletal muscle and frequent nerve fibres. The main lesion was within the glandular tissue and was surrounded by smaller islands with similar histological characteristics (**Figure 1**). These lesions were composed of canalicular structures with a central lumen and were branching and anastomosing (**Figure 2A**). These foci were covered by one or two layers of cuboidal to columnar epithelial cells with vesicular nuclei and inconspicuous nucleoli. No cytological pleomorphism or mitotic figures were observed.

The tumour cells were arranged in a loose, otherwise paucicellular stroma with a prominent vascular pattern (**Figure 2B**). The stroma was PAS-positive and metachromatic with toluidine blue (**Figure 3A** and **3B**). Secretory intralobular ducts were dilated.

The tumour cells were positive for AE1/AE3, S-100 and CD117 (**Figure 4A** and **4B**). Expression of p63 (a selective marker of myoepithelial and basal cells in stratified epithelia) was negative, as was α-SMA, vimentin, and the proliferation marker Ki 67. Given these microscopic and immunohistochemical findings, a diagnosis of multifocal canalicular adenoma was made. At the time of writing, there has been no recurrence of the lesion.

Discussion

Salivary gland tumours are relatively uncommon in comparison with other tumours. Although they represent less than 2% of all neoplasias and 2-6.5% of all head and neck neoplasias, these tumours are of particular interest, given their varied histological and clinical characteristics [12-16].

Despite originating from the same progenitor cells, tumours of the minor salivary glands (approximately 14-22% of all salivary gland tumours) have a tendency to develop in particular sites, and thereby exhibit different biological behaviour. Although the majority of tumours involve the palate (due to its numerous glands), in the case of CA, it is most commonly located in the upper lip (80% of cases) [5, 7, 12, 17].

The most common presentation of epithelial tumours of the minor salivary glands is as a simple nodule. However, CA affecting the upper lip may occasionally present multifocally [6]. Rousseau *et al*. [18] have proposed that multifocal variants be classified into three categories according to their growth pattern (clinical, microscopic and recurrent). These authors believe that recurrent tumours most likely represent growth of microscopic foci, which persisted following resection of larger, clinically-evident tumours. In this case, although the multifocal tumour was completely removed by excision biopsy, conferring an excellent prognosis [5], we recognise that patients should receive long-term follow-up (up to 11 years) since multifocal lesions have higher rates of local recurrence, albeit without malignant transformation [2, 6].

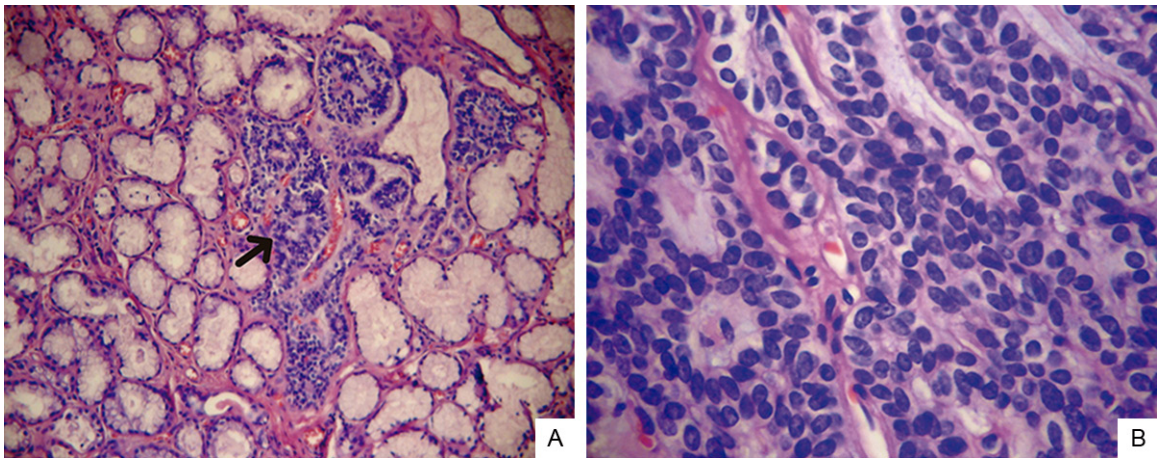

Figure 2. Multifocal canalicular adenoma of the upper lip. A. Interconnecting and branching canal-like structures (Arrow). H/E. Original magnification ×200; B. Branching and interconnecting tubules lined in a nearly acellular stroma. H/E. Original magnification ×400.

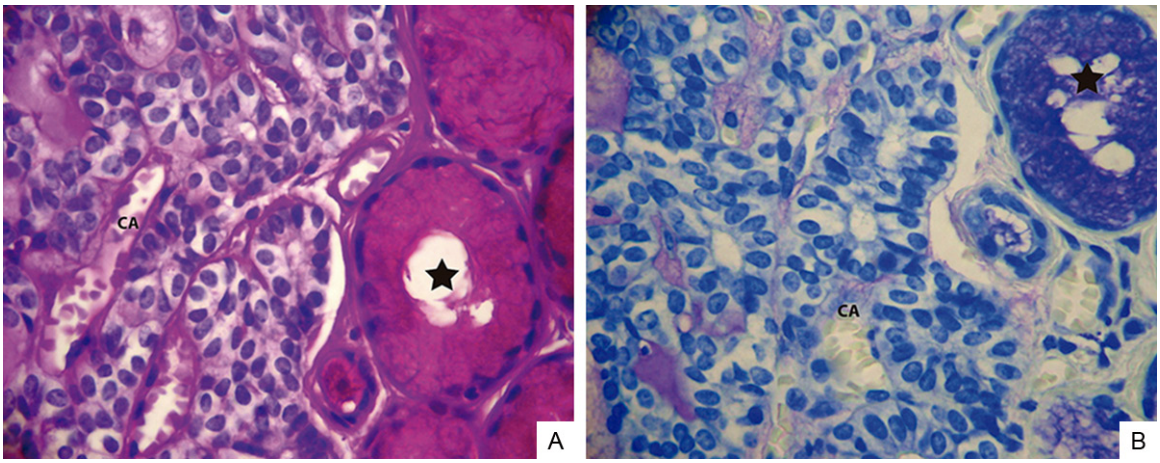

Figure 3. Multifocal canalicular adenoma of the upper lip. A. Canalicular adenoma (CA). Mucous acini strongly PAS positive (star). PAS/H; B. Canalicular adenoma (CA). Mucous acini strongly metachromatic (star). Toluidine blue pH 3.8. Original magnification ×400.

Although the clinical details in this report correspond to those predicted by the literature as most frequent for CA (sex, age, and location), this tumour has been described as a rare entity, relatively unknown to practising dental surgeons, and its histological diagnosis and clinical management can therefore be difficult [19]. Matsuzaka *et al.* [20] reported that from 18,093 oral biopsies carried out between 1996 and 2004 in Tokyo Dental College, only one case of CA was identified. In addition, the clinical characteristics of CA, its firm or slightly fluctuant consistency and occasionally blue-tinged mucosa may imitate a mucocele, a lesion which is much more common and (in contrast to CA) usually develops in the lower lip [18, 21].

Other differential diagnoses include benign and malignant neoplasias of glandular tissue, sialolithiasis with secondary sialadenitis, vascular anomalies and even lipomas [19]. It has been stressed that CA must be clearly differentiated from polymorphous low-grade adenocarcinoma (PLGA) and adenoid cystic carcinoma (ACC), since it's similar histological features may lead to an overdiagnosis with excessive surgery and radiotherapy [2].

In agreement with Sivolella *et al*. [19], the histological features identified in our case are typical of CA; importantly however, these features have also been observed in some adenocarcinomas, meaning that immunohistochemical

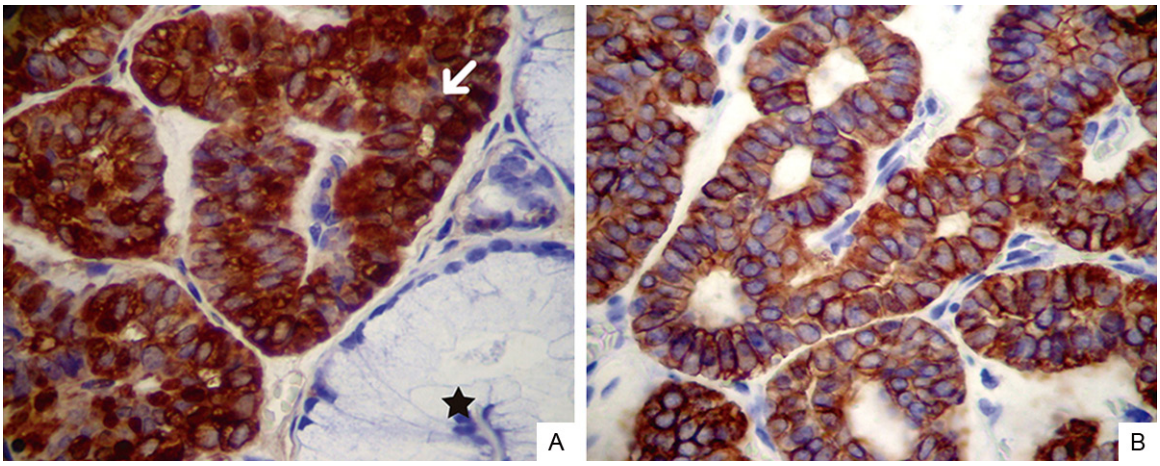

Figure 4. Multifocal canalicular adenoma of the upper lip. A. Inmunohistochemical intense staining for S-100 in the tumour cells (arrow). Mucous acini negative (star). S-100; B. Tumour cells reactive for cytokeratin. Pancytokeratin AE1/AE3. Original magnification ×400.

studies are necessary in order to confirm the diagnosis. In our case, the immunological profile of CA was confirmed by positivity for pancytokeratin AE1/AE3, CD117, and S-100 protein. This indicated a probable origin in the luminal epithelial cells of secretory ducts or the intercalated duct cells [3, 5, 11, 22]. The lack of p63 and α-SMA reactivity excluded myoepithelial origin [22, 23], and negativity for vimentin precluded a diagnosis of PLGA according to the majority of reports [6, 24]. Negativity for Ki 67 was compatible with a benign neoplasia, as some authors have reported [2, 19].

CA is included in the group of salivary gland adenomas by the WHO, and its most important differential diagnoses are ACC and basal cell adenoma (BCA). In addition, its multifocal and cribriform patterns should not be interpreted as evidence of malignancy. BCA is a rare benign epithelial neoplasia characterised by a predominance of basaloid cells, without the chondromyxoid component of pleomorphic adenomas [5]. Although the major salivary glands represent its most frequent site (parotid: 75%, submandibular gland: 5%), some reports suggest that when rarely seen in the minor salivary glands, it has a predilection for the upper lip [5, 15, 25]. Immunohistochemistry has now established that CA develops from luminal ductal cells whereas BCA is originated in the salivary gland parenchyma [6]. BCA is positive for p63, α-SMA, cytokeratins and EMA, supporting its ductal and myoepithelial differentiation, while CA shows pure luminal ductal cell differentiation [11, 25]. Importantly, hybrid forms of CA and BCA have also been reported by WHO.

Interestingly, Furuse *et al.* [24] report that although the differential diagnosis of CA most commonly includes BCA, distinguishing these two entities has minimal therapeutic significance, when compared with differentiating PLGA, a lesion of greater clinical importance. This malignant entity is locally aggressive and often has a histological pattern identical to CA, yet it requires a very different surgical approach. PLGA is the second most frequent malignant tumour of the minor salivary glands, and although its preferred location is the palate (60%), there are reports of cases involving the upper lip [7]. PLGA shares clinical similarities with CA, given its mean age of presentation (59 years) and female predominance (2:1). These underscore the need for reliable methods when considering the differential diagnosis [7, 11, 15].

PLGA develops from intercalated duct cells and microscopically it shows a varied architecture, uniform cells and nuclei, frequent perineural invasion and a low metastatic potential. It is non-encapsulated, always invades adjacent tissues, and within the same tumour there may be different patterns of growth not always appreciated in an incisional biopsy [24]; the predominance of the canalicular form can erroneously be diagnosed as CA. Matsuzaka *et al.* [20] point out that where CA is resected in a fragmented way or has a cystic structure, it may be misinterpreted as PLGA. A diagnosis of PLGA is con-

firmed by immunohistochemistry showing positivity for p63, α-SMA, and vimentin. Furuse *et al.* [24] claim that in isolated cases CA may overlap with areas of BCA. This would justify the presence of occasional small foci of vimentin-positive cells, clearing this great diagnostic difficulty. The same authors clarify that PLGA is always negative for CK13 while CA may express it, and that S-100, a test normally requested by pathologists to identify salivary gland tumours, is not that useful in differentiating CA from PLGA, given that both would be positive.

Despite no critical differences in management, the characteristics of PLGA should to be compared with the cribriform pattern of ACC. Although ACC is a malignant glandular neoplasia which shows a more aggressive behaviour (usually with perineural invasion) and frequently involves the sinonasal cavity, its involvement of minor salivary glands and appearance in the upper lip (more common in the lower) have been reported [5, 7]. It is distinguished from CA by its cribriform architecture with characteristic microcystic spaces filled with a mucoid substance and a poorly-vascularised stroma. The neoplastic cells are epithelial and myoepithelial in nature, clearly differentiated by immunohistochemical stains [11].

Other diagnostic dilemmas have been reported regarding this tumour. It has been reported that CA may be confused with papillary cystadenocarcinoma [26], given its tendency to show a large single cyst or multiple small cysts, and its consequent papillary projections. These however, usually locally infiltrate the glandular parenchyma and surrounding connective tissue. The presence of fragmented cysts with haemorrhagic foci and granulation tissue is a common finding [5, 20].

The importance of an adequate differential diagnosis of nodular lesions in the oral mucosa has been emphasised; we agree with Stramandinoli-Zanicotti *et al*. [6]. In that although clinical details, aspiration biopsies and routine histopathology may provide valuable information, the definitive diagnosis of CA should only be established through immunohistochemical studies. In this way, the clinical and surgical findings may be confirmed and potential diagnostic errors avoided.

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Mario Cantín, CIMA Research Group, Faculty of Dentistry, Universidad de La Frontera, Avenue Manuel Montt 112, Temuco, Chile. Tel*:* 056-45-2325574; E-mail: mario.cantin@ufrontera.cl

References

[1] Siqueira CS, Fernandes KS, Vivas AP, Pinto Ddos S Jr, de Sousa SC. Clinical and histological features of multifocal canalicular adenomas of the upper lip. Braz Dent J 2013; 24: 542-546.

[2] Tyralik D, Dzierwa-Gawron A, Ryś J. Canalicular adenoma of the upper lip. Metachronous (multifocal) canalicular adenoma of the upper lip: a case report of an unusual finding. Pol J Pathol 2013; 64: 71-74.

[3] Huebner TA, Almubarak H, Drachenberg CB, Papadimitriou JC. Canalicular adenoma--search for the cell of origin: ultrastructural and immunohistochemical analysis of 7 cases and review of the literature. Ultrastruct Pathol 2014; 38: 74-82.

[4] Smullin SE, Fielding AF, Susarla SM, Pringle G, Eichstaedt R. Canalicular adenoma of the palate: case report and literature review. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004; 98: 32-36.

[5] World Health Organization: Classification of Tumours. Pathology and Genetics of Head and Neck Tumours. In: Barnes L, Everson JW, Reichart P, editors. Lyon: IARC Press; 2005.

[6] Stramandinoli-Zanicotti RT, Cesa TS, Giustina JD, Bahr JA, Schussel JL, Sassi LM. Canalicular adenoma of the minor salivary gland in the upper lip: case report. J Oral Diag 2012; 1: 4-6.

[7] Yih WY, Kratochvil FJ, Stewart JC. Intraoral minor salivary gland neoplasms: review of 213 cases. J Oral Maxillofac Surg 2005; 63: 805-810.

[8] Dayisoylu EH, Pampu AA, Mungan S, Taskesen F. Intra-mandibular canalicular adenoma: report of a rare case. J Pak Med Assoc 2012; 62: 1239-1241.

[9] Grimm EE, Rulyak SJ, Sekijima JH, Yeh MM. Canalicular adenoma arising in the esophagus. Arch Pathol Lab Med 2007; 131: 1595-1597.

[10] Maamouri F, Bellil K, Bellil S, Chelly I, Mekni A, Kchir N, Haouet S, Zitouna M. Canalicular adenoma of buccal mucosa. Pathologica 2007; 99: 69-70.

[11] Ellis GL, Auclair PL. Tumors of the salivary glands: AFIP Atlas of tumor pathology, series 4. Washington: Armed Forces Institute of Pathology (AFIP); 2008.

[12] Bansal AK, Bindal R, Kapoor C, Vaidya S, Singh HP. Current concepts in diagnosis of unusual

salivary gland tumors. Dent Res J (Isfahan) 2012; 9: S9-S19.
[13] Avila RE, Samar ME, Ferraris L, Ferraris RV, Fonseca I, Corball A, Asís OG, Olmedo L. Non-Hyalinizing Clear Cell Carcinoma of the Parotid: Report of Two Cases with Different Grade of Differentiation. Int J Morphol 2013; 31: 1056-1061.
[14] Laishram RS, Kumar KA, Pukhrambam GD, Laishram S, Debnath K. Pattern of salivary gland tumors in Manipur, India: A 10 year study. South Asian J Cancer 2013; 2: 250-253.
[15] Samar ME, Avila RE. Tumores epiteliales de glándulas salivales. Saarbrücken: Editorial Académica Española; 2013.
[16] Sunil S, Gopakumar D. Pleomorphic Adenoma: A Case Report and Review of Literature. Int J Odontostomat 2013; 7: 171-174.
[17] Pereira MC, Pereira AA, Hanemann JA. Immunohistochemical profile of canalicular adenoma of the upper lip: a case report. Med Oral Patol Oral Cir Bucal 2007; 12: E1-3.
[18] Rousseau A, Mock D, Dover DG, Jordan RC. Multiple canalicular adenomas: a case report and review of the literature. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 1999; 87: 346-350.
[19] Sivolella S, Valente M, De Biagi M, Mazzoleni S, Stellini E. Canalicular adenoma immunoprofile: a case report. Gerodontology. 2013; [Epub ahead of print].
[20] Matsuzaka K, Murakami S, Shimono M, Inoue T. Canalicular adenoma arising in the upper lip: review of the pathological findings. Bull Tokyo Dent Coll 2004; 45: 229-233.
[21] Chen YK, Lin CC, Lai S, Chen CH, Wang WC, Lin YR, Hsue SS, Lin LM. Pleomorphic adenoma with extensive necrosis: report of two cases. Oral Dis 2004; 10: 54-59.
[22] Oliveira-Santos C, Freitas-Faria P, Damante JH, Consolaro A. Asymptomatic nodules of the upper lip: report of a canalicular adenoma with immunoprofile presentation. Gerodontology 2012; 29: e1121-e1124.
[23] Edwards PC, Bhuiya T, Kelsch RD. Assessment of p63 expression in the salivary gland neoplasms adenoid cystic carcinoma, polymorphous low-grade adenocarcinoma, and basal cell and canalicular adenomas. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2004; 97: 613-619.
[24] Furuse C, Tucci R, Machado de Sousa SO, Rodarte Carvalho Y, Cavalcanti de Araújo V. Comparative immunoprofile of polymorphous low-grade adenocarcinoma and canalicular adenoma. Ann Diagn Pathol 2003; 7: 278-280.
[25] Samar ME, Avila RE, Fonseca I, Ferraris RV, Rabino M. Adenoma de células basales de glándulas salivales, variedades sólido y tubular: estudio histopatológico e inmunohistoquímico. Patología (Rev Latinoamer Mx) 2008; 46: 276-283.
[26] Velasco I, Salinas F, Aguilar L, Gallego A, Pastrián J, Fariña R, Soto R, Mebus C, Zurbuchen A. Anatomical Considerations in Parotidectomy: Review of the Literature and Case Report. Int J Morphol 2013; 31: 231-238.