Annals of Diagnostic Pathology 18 (2014) 5–9

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

Original Contribution

# Basal cell adenoma of salivary glands with a focal cribriform pattern: clinicopathologic and immunohistochemical study of 19 cases of a potential pitfall for diagnosis☆,☆☆,★

Bin-bin Li, DDS, PhD *,[1], Chuan-xiang Zhou, DDS, PhD [1], Sheng-nan Jia, DDS

*Department of Oral Pathology, Peking University School and Hospital of Stomatology, Beijing, PR, China*

ARTICLE INFO

*Keywords:*
Basal cell adenoma
Adenoid cystic carcinoma
Cribriform
Clinicopathologic feature
Immunohistochemistry

ABSTRACT

Cribriform type of salivary basal cell adenoma (cBCA) is relatively rare and problematic in distinction from adenoid cystic carcinoma (AdCC). The aim of this study was to investigate the clinicopathology and immunoprofile of cBCA. Nineteen cases of cBCA with at least a 30% area of cribriform structure under microscope were analyzed by the description of their histopathologic and immunohistochemical features using the antibodies of matrix metalloproteinase-9 (MMP9), CK8&18, calponin, SMA, S100, P63, CD117, and laminin. The patients of cBCA ranged from 24 to 71 years with a distinct predilection for females (79%). The tumor was well-circumscribed and had no recurrent tendency after a local excision followed by a median of 67 months. Enhanced computed tomography (CT) showed that the tumor was rich in blood supply. Microscopically, it was mainly composed by the basaloid cells with the peripheral palisading. The cells around the cribriform pattern expressed P63 protein and had almost no immunoreactivity for calponin, SMA, S100, or CK8&18. The expression level of MMP9, laminin, and CD117 were significantly lower in cBCA than those in AdCC. Good circumscription, lack of infiltrative properties, and absence of MMP9, laminin, CD117, and myoepithelial marker (SMA, S100 and calponin) in the cells around the cribriform spaces, are the most reliable points for differential diagnosis of cBCA from AdCC.



## 1. Introduction

Basal cell adenoma (BCA) was first described by Kleinsasser and Klein in 1967 [1]. It's a rare benign neoplasm characterized by the basaloid appearance of the tumor cells [2]. Nagao [3] first reported that some BCAs have cribriform patterns, pseudocysts of amorphous, basophilic material characteristic of adenoid cystic carcinoma (AdCC), which is a very difficult problem for differential diagnosis. Then Dardick [4] described this kind of adenoid cystic pattern or solid-cribriform type of BCA in 1992. Recently, 18 cases of cribriform BCA (cBCA) were reported having most of the clinicopathologic features of conventional BCA [5]. However, because of its rarity, more extensive review of this pattern is necessary.

The aims of this study were to analyze the clinicopathologic features and prognosis of cBCA with cribriform component and to compare the microscopic characteristics of cribriform pattern between cBCA and AdCC using matrix metalloproteinase-9 (MMP9), calponin, SMA, S100, P63, CK8&18, CD117 and laminin antibodies. It would allow clinicians to better understand the intrinsic quality of cBCA and choose an appropriate treatment.

## 2. Materials and methods

The patients fulfilling the following criteria were included in our study: (i) a well-circumscribed tumor composed of the peripheral-palisading basaloid cells. (ii) cribriform patterns accounted for more than 30% in the tumor. Thus, a group of 19 cases from a total of 261 cases diagnosed as cBCA was retrieved from the files of Oral Pathology Department, Peking University School and Hospital of Stomatology from 1985 to 2012. All tissues were obtained in accordance with the protocols approved by Ethics Committee of Peking University Health Science Center. The surgical specimens were fixed in formalin, routinely processed, and embedded in paraffin. The histologic materials from the tumors were reviewed on the hematoxylin-eosin-stained sections by two experienced pathologists to confirm the accuracy of the diagnosis. The investigated parameters included the age at the time of diagnosis, the anatomical location, the imaging findings, the histological type, the treatment and the prognosis. Additionally, 10 cases of AdCC were chosen as contrasts.

☆ The author has no relevant financial interest in the products or companies described in this article.

☆☆ Declaration of Conflicting Interests: The author declared no potential conflicts of interest with respect to the authorship and/or publication of this article.

★ Funding: The author received no financial support for the research and/or authorship of this article.

* Corresponding author. Department of Oral Pathology, Peking University School and Hospital of Stomatology, 22 Zhongguancun Avenue South, Haidian District, Beijing 100081, P.R. China. Tel.: +86 10 82195221; fax: +86 10 82193402.

*E-mail address:* kqlibinbin@aliyun.com (B. Li).

[1] Contributed equally.

1092-9134/$ – see front matter © 2014 Elsevier Inc. All rights reserved.
http://dx.doi.org/10.1016/j.anndiagpath.2013.09.002

**Table 1**
The antibodies used for the immunohistochemical evaluation

| Antibody | Clone | Pretreament | Dilution | Source |
|---|---|---|---|---|
| MMP9 | ZA-0336 | None | Ready to use | Zymed, Carlsbad, CA |
| Calponin | ZA-0524 | Citrate HIER | 1:100 | Zymed, Carlsbad, CA |
| SMA | ZA-0003 | None | Ready to use | Zymed, Carlsbad, CA |
| S100 | ZA-0224 | Citrate HIER | Ready to use | Zymed, Carlsbad, CA |
| P63 | ZM-0406 | Citrate HIER | 1:100 | Zymed, Carlsbad, CA |
| CK8&18 | ZM-0315 | Pepsin(10 min) | Ready to use | Zymed, Carlsbad, CA |
| CD117 | ZM-0437 | Citrate HIER | Ready to use | Zymed, Carlsbad, CA |
| Laminin | ZM-0181 | Trypsin (20 min) | Ready to use | Zymed, Carlsbad, CA |

The immunohistochemical staining was performed using a standard streptavidin-biotin-peroxidase complex method. Calponin, SMA, S100, MMP9, P63, CK8&18, CD117, and laminin antibodies were purchased from Zymed Laboratories (South San Francisco, CA, USA) (Table 1). The antibodies of MMP9, CK8&18, SMA, S100, and laminin were used for single staining by LAB-SA kit. Calponin (only myoepithelial cell is positive to) and P63 (both myoepithelial cell and basaloid cell are positive to) antibodies were used for the double staining by Polink DS-MR-Hu A1 kit, a simultaneous polymer double staining kit for mouse and rabbit antibody with DAB and AP-Red Plus [6]. We purchased LAB-SA kit and Polink DS-MR-Hu A1 kit from Golden Bridge International Labs (Mukilteo, WA, USA). Two experienced pathologists respectively judged the immunohistochemical results.

## 3. Results

### 3.1. Clinical data

Nineteen cases of cBCA included 15 women and 4 men. The age at the time of diagnosis ranged from 24–71 years (average, 48 years). They all affected the parotid glands. The clinical symptom was only local swelling without pain. The enhanced CT revealed a well-defined solid mass that was rich in vascular (Fig. 1). The complete surgical removal with an extracapsular limit was performed. Grossly, the sizes of the tumors ranged from 0.8 to 5cm with the complete encapsulations (Fig. 2).

The follow-up data were available for all 19 patients ranging from 5 months to 276 months, with a median of 67 months (Table 2). The patient had a satisfactory postoperative period, and presented no sign of local recurrence after surgery until this paper was summarized (March, 2013).

### 3.2. Microscopic findings

The gross specimen of cBCA showed a well-encapsulated mass with a varied pattern. Generally, the well-defined capsules were very evident, and some of the tumors tended to separate entirely from the capsule after dissection. Not any kind of perineural or perivascular invasion was presented in the tumor (Fig. 3A, B).

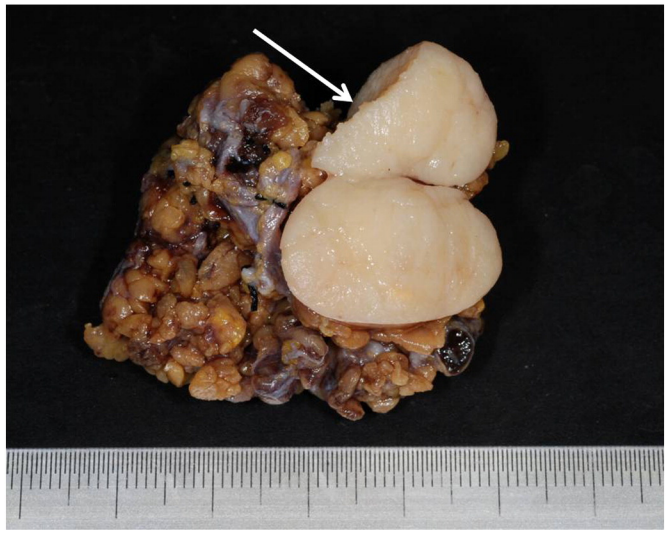

**Fig. 2.** The tumor showed an intact capsule and had a very clear boundary with the surrounding gland. (The white arrow indicates the defected part because of a frozen biopsy.)

Microscopically, there were areas of cellularity with the cribriform, trabecular-tubular and solid patterns in cBCA. These patterns may coexist in the same tumor, but one pattern usually predominated. No membranous subtype was found in any case. All 19 cases shared a striking architectural appearance resembling the cribriform pattern in AdCC. Some basaloid epithelial nests were enlarged or distorted by small to moderately sized intercellular clear spaces which were enclosed by an outer palisaded layer, resulting in the cribriform spaces (Fig. 3C). No atypia cells or mitotic activity were found. The tumors cells around the cribriform spaces consisted of uniform cells with the basaloid appearance, eosinophilic cytoplasm and oval nuclei. In the solid area, there were large islands with peripheral cells that may be more hyperchromatic and palisading. The trabecular-tubular pattern formed cords and ductal structures. The stroma was usually scanty.

As far as AdCC was concerned, it exhibited an invasive growth capacity consistent with aggressive clinical behavior. These tumors were typically unencapsulated or poorly defined, and infiltrative (Fig. 3D). They could invade the surrounding muscle tissue (Fig. 3E). The perineural or even intraneural invasion could be observed in AdCC (data not shown). The proliferating cell was a

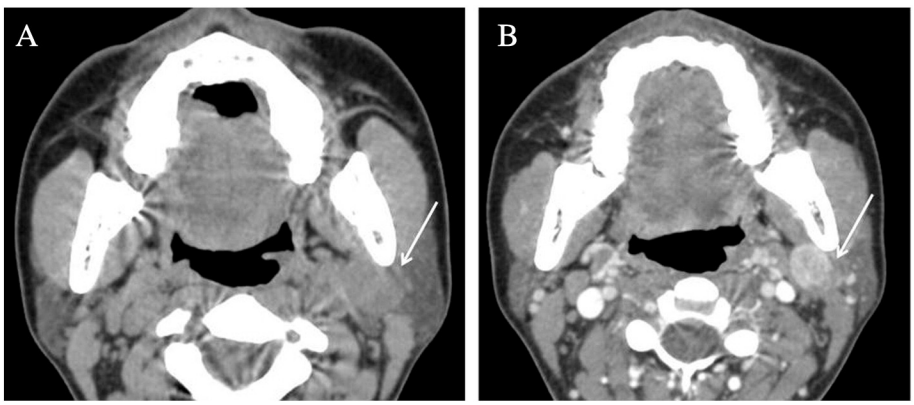


**Fig. 1.** The radiological appearance of cBCA. (A) CT showed a well-defined mass in the parotid region. (B) Enhanced CT suggested the tumor abundant in blood supply. The white arrow notes the tumor.

**Table 2**
The clinical features of the salivary cribriform variant of basal cell adenoma (n = 19)

| Case | Age (y) | Gender | Location | Current status/follow-up (months) |
|---|---|---|---|---|
| 1 | 64 | F | Parotid gland | NSR/276 |
| 2 | 59 | F | Parotid gland | NSR/120 |
| 3 | 51 | M | Parotid gland | NSR/114 |
| 4 | 33 | F | Parotid gland | NSR/69 |
| 5 | 52 | F | Parotid gland | NSR/60 |
| 6 | 24 | M | Parotid gland | NSR/45 |
| 7 | 71 | F | Parotid gland | NSR/41 |
| 8 | 50 | F | Parotid gland | NSR/37 |
| 9 | 54 | F | Parotid gland | NSR/36 |
| 10 | 34 | F | Parotid gland | NSR/35 |
| 11 | 58 | F | Parotid gland | NSR/34 |
| 12 | 32 | F | Parotid gland | NSR/30 |
| 13 | 47 | M | Parotid gland | NSR/29 |
| 14 | 49 | F | Parotid gland | NSR/5 |
| 15 | 35 | F | Parotid gland | NSR/9 |
| 16 | 62 | F | Parotid gland | NSR/16 |
| 17 | 34 | F | Parotid gland | NSR/96 |
| 18 | 45 | F | Parotid gland | NSR/111 |
| 19 | 60 | M | Parotid gland | NSR/119 |

Note: M, male; F, female; NSR: no symptoms of recurrence.

small cuboidal cell with a round hyperchromatic nucleus and scant cytoplasm. Mitotic activity, pleomorphism, and cellular atypia were not usually presented(Fig. 3F). The cells were arranged in various patterns that had been described as cribriform, tubular, and solid. In order to compare in parallel with cBCA, the cribriform pattern predominated in these series of AdCC, but the tubular or solid area may coexist in the same tumor. In the cribriform area, islands of cells formed pseudocystic spaces which were surrounded by basophitic, mucinous, or hyalinized material representing replicated basal lamina. The tubular pattern showed the cells in ductal arrangement with a single lumen. The solid pattern had broad sheets and solid islands of the small, dark-staining cells. The stroma in AdCC was fibrous.

### 3.3. Immunohistochemical findings

Immunohistochemically, all cells around the cribriform structures showed no reactivity for MMP9 (Fig. 4A). P63-positive and calponin-negative cells were found in the cribriform pattern of cBCA, although the tumor cells exhibited some degree of myoepithelial cell participation (calponin-positive) in other areas such as solid and trabecular-tubular area. The cells around the cribriform structure in cBCA were almost devoid of staining with calponin, SMA, S100, and CK8&18 (Fig. 5A-D). Lamin protein was faintly or negatively expressed in the cribriform patterns of cBCA (Fig. 6A).

In contrast, the cells around the cribriform structure in AdCC were partially MMP9-positive (Fig. 4B). Calponin and P63 protein were both detected in the cribriform pattern (Fig. 5E). However, SMA and S100 were faintly or negatively expressed there. Some SMA/S100-positive nests appeared in the solid area (Fig. 5F,G). The inner layer of the cribriform pattern in AdCC showed positive immunoreactivity for CK8&18 (Fig. 5H). The substrate-like substances were revealed clearly by the lamin stain (Fig. 6B). CD117 was expressed strongly in some AdCC but no staining in cBCA (Fig.7).

## 4. Discussion

Basal cell adenoma is the third most common of the benign parotid tumors, although its incidence is as low as accounting for 1% to 4% of all salivary gland tumors [7]. Nagao [3] reported that the incidence of BCA was 7.5% among 531 cases of primary epithelial tumors of the parotid gland, and adenoid cystic pattern accounted for 10% in BCA. Our data suggested that the percentage of cBCA was 7% (19/261). Basal cell adenoma can occur at any age but it happens most commonly in middle-aged and older adults with prevalence in the seventh decade of life [8]. Our data showed that cBCA had a female tendency.

The characteristics of BCA such as the integrity of the basal layer, decreased number of mitoses, and slow growth pattern are the typical characteristics of a benign lesion. From our findings, we could

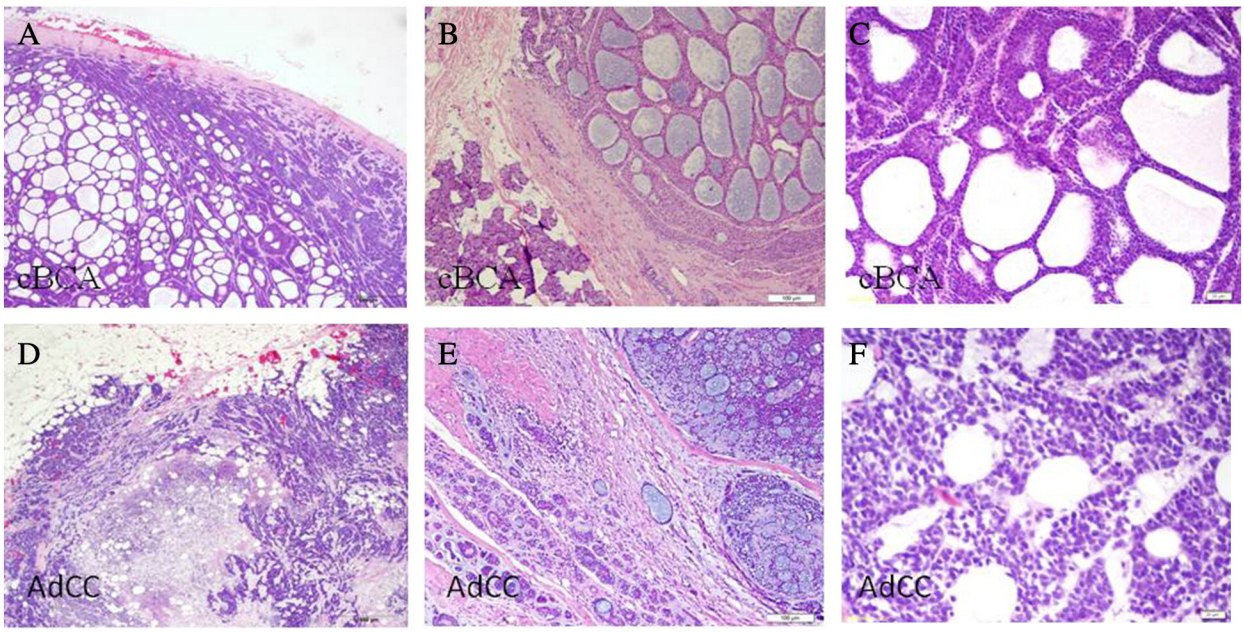


**Fig. 3.** Histological aspects of the cribriform pattern in cBCA (A-C) and AdCC (D-F) (H&E). (A) cBCA was well encapsulated with the cribriform components. (B) A distinct capsule was observed between the tumor nests and the adjacent salivary glands in cBCA. The tumor islands consisted of basaloid cells with columnar, palisading cells at the periphery. (C) The small basaloid tumor cells around the cribriform area of cBCA were confluent but interspersed with many variably sized and shaped intercellular spaces. They were palisaded at the margins of the isolated nests. (D) An AdCC showed its infiltrative character. (E) An AdCC was poorly defined or non-encapsulated, invading the surrounding muscle tissue. (F) The classic cribriform pattern of AdCC appeared small, cuboidal cells with hyperchromatic nuclei. The cells were uniform. The spaces contained a basophilic and mucoid material.

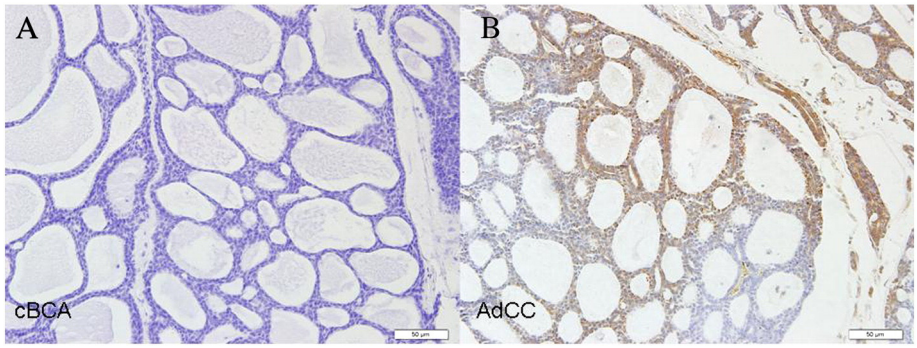


**Fig. 4.** The lining cells around the cribriform pattern of cBCA (A) didn't express MMP9 protein, while those in AdCC (B) partially expressed MMP9.

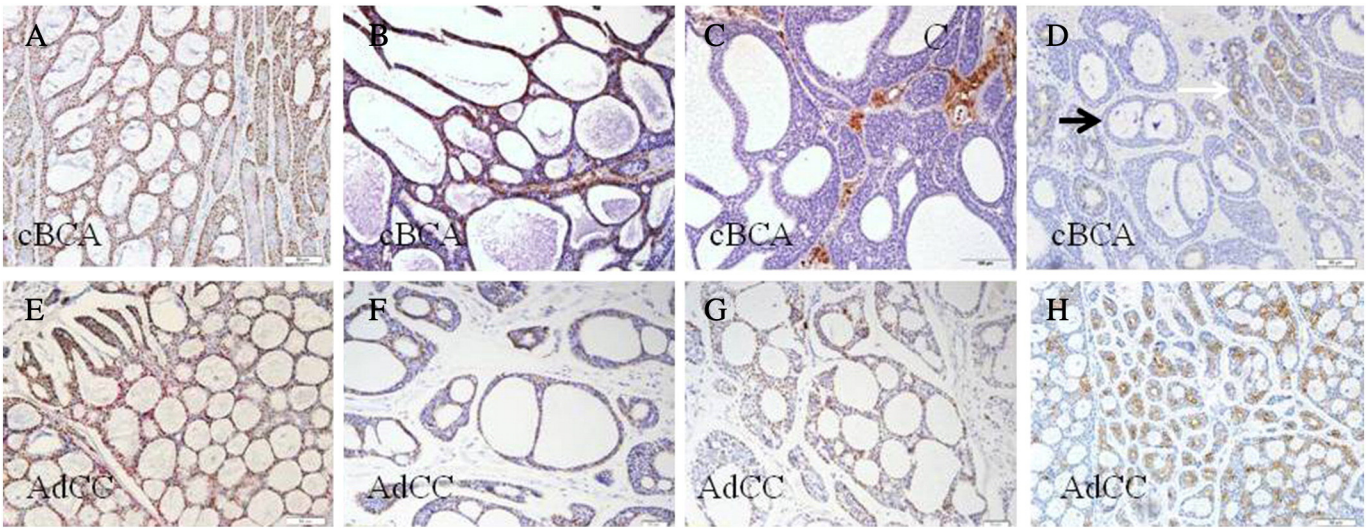


**Fig. 5.** Immunoreactivity for P63, calponin, SMA, S100, and CK8&18 in the cribriform pattern of cBCA (A-D) and AdCC (E-H). (A, E) The double staining for calponin (red in cytoplasm) and P63 (brown in nucleus). (A) cBCA had no immunoreactivity for calponin in most cribriform patterns but revealed P63-positive strongly. (E) AdCC in the cribriform variant exhibited positively for both calponin and P63 suggesting some degree of the myoepithelial cell participation in AdCC. There were no positive staining for SMA (B, F) and S100 (C,G) in cBCA (B, C) and AdCC (F,G). (D) The cells around the cribriform patterns of cBCA had no immunoreactivity for CK8&18 (black arrow), whereas the adjacent tubular area expressed the cytoplasmic immunoreactivity for it (white arrow). (H) CK8&18 was expressed in the inner layer of the cribriform pattern in AdCC.

conclude that the cribriform pattern was not the differential points for cBCA and AdCC. The distinction points between cBCA and AdCC were the intactness of the capsule and the outer palisaded cells in cBCA as well as the invasive growth pattern in AdCC. Additionally, the vascular-rich appearance of enhanced CT was also valuable for the diagnosis. True invasion must be distinguished from both multinodularity with a pushing type of growth pattern and multifocal origin in adjacent salivary lobules.

It was reported that BCA exhibited some degree of myoepithelial cell participation [8] with the periductal, epithelioid, and spindled (stromal-like) morphologic structures [9]. We did find the myoepithelial marker-positive cells in other areas of cBCA except the cribriform area. But the cells around the cribriform pattern in cBCA were almost devoid of staining with the calponin, SMA, S100, and CK8&18, suggesting that they were composed largely of basaloid cells. We speculated that these cells originated from the basal layers of the intercalated duct or the terminal duct.

Distinction of BCA with cribriform areas and AdCC of salivary glands can be problematic. In this study we have found that the most reliable features that help separate the two conditions include good

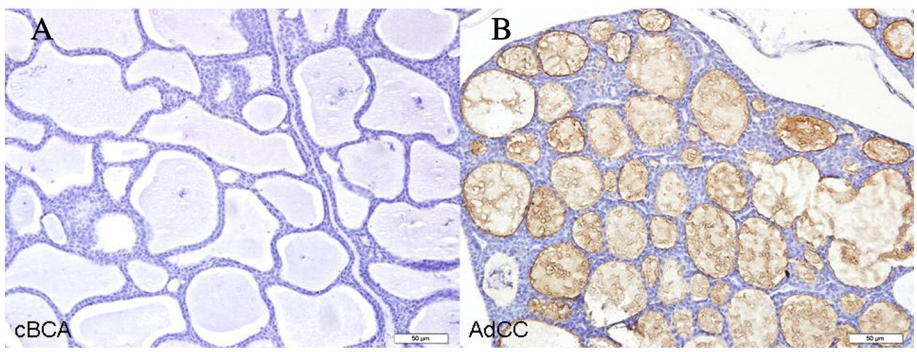


**Fig. 6.** The cells around the cribriform structure negatively exhibited lamin in cBCA (A). In contrast, the counterpart in AdCC was strongly positive to the lamin antibody (B).

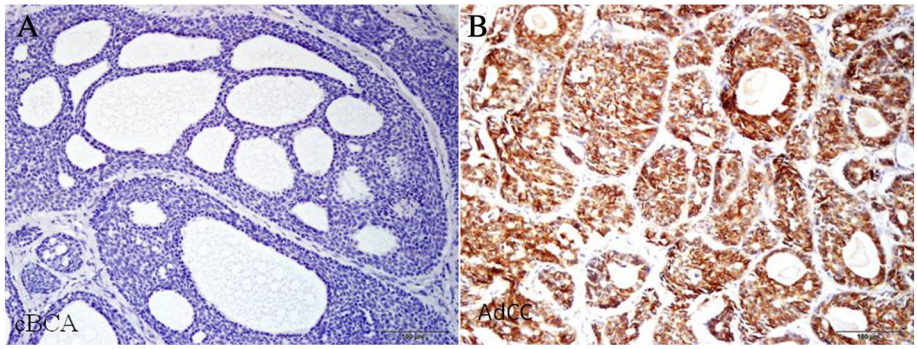


**Fig. 7.** Most cells around the cribriform pattern in cBCA (A) showed no immunoreactivity for CD117, but some AdCC presented strong positive staining there (B).

circumscription and lack of invasive properties in cBCA and absence of staining for MMP9 and laminin in the cells around the cribriform spaces in cBCA, and of calponin, SMA, or S100 in the cribriform areas in contrast with AdCC.

## References

[1] Kleinsasser O, Klein HJ. Basalzelladenoma der speicheldrusen: Arch Klin Exp Ohren-Nasen-Kehlkopfheilk 1967;189: 302–16.
[2] Cardesa A, Zidar N, Nadal A, Ereno C. Basal cell adenoma. In: Barnes L, Eveson JW, Reichart P, Sidransky D, editors. World health organization classification of tumours: pathology and genetics of tumours of the head and neck. Lyon, France: IARC Press; 2005.
[3] Nagao K, Matsuzaki O, Saiga H, et al. Histopathologic studies of basal cell adenoma of the parotid gland. Cancer 1982;50:736–45.
[4] Dardick I, Lytwyn A, Bourne AJ, Byard RW. Trabecular and solid-cribriform types of basal cell adenoma. A morphologic study of two cases of an unusual variant of monomorphic adenoma. Oral Surg Oral Med Oral Pathol 1992;73:75–83.
[5] Tian Z, Hu Y, Wang L, Li L, Zhang C, Li J. An unusual cribriform variant of salivary basal cell tumours: a clinicopathological study of 22 cases. Histopathology 2012;61:921–9.
[6] De Pasquale A, Paterlini P, Quaglino D. Immunochemical demonstration of different antigens in single cells in paraffin-embedded histological sections. Clin Lab Haematol 1982;4:267–72.
[7] Kawata R, Yoshimura K, Lee K, Araki M, Takenaka H, Tsuji M. Basal cell adenoma of the parotid gland: a clinicopathological study of nine cases—basal cell adenoma versus pleomorphic adenoma and Warthin's tumor. Eur Arch Otorhinolaryngol 2010;267:779–83.
[8] Regesi JA, Sciubba JJ. Salivary gland diseases in oral pathology. Philadelphia, PA: Saunders; 1993. p. 270–1.
[9] Zarbo RJ, Prasad AR, Regezi JA, Gown AM, Savera AT. Salivary gland basal cell and canalicular adenomas. Immunohistochemical demonstration of myoepithelial cell participation and morphogenetic considerations. Arch Pathol Lab Med 2000;124: 401–5.