RESEARCH ARTICLE

Gray scale and doppler ultrasonography features of the carcinoma ex pleomorphic adenoma

¹Ding Angang, ¹Li Jia, ¹Gong Xia, ¹Xiong Ping and ²Li Jiang

¹Department of Ultrasound, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiao tong University, Shanghai, PR China; ²Department of Pathology, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiao tong University, Shanghai, PR China

Objectives: For lesions in the salivary glands, ultrasonography (US) is an ideal tool for initial assessment. The aim of this study was to characterize and differentiate between the Gray scale and Doppler US findings of intracapsular carcinoma ex pleomorphic adenoma (Ic-CxPA) and invasive carcinoma ex pleomorphic adenoma (Inv-CxPA).

Methods: A total of 87 patients (89 lesions) with histopathologically proven CxPA underwent US examination. The following characteristics were assessed on US images: size, shape, border, echogenicity, echo texture, posterior echo, vascularity, and regional lymph node enlargement. One-way analysis of variance (ANOVA), nonparametric test, Fisher's exact test, chi-square test and receiver operating characteristic (ROC) curve were used for the analyses of the US findings of Ic-CxPAs and Inv-CxPAs.

Results: We found that on US images, nearly all Ic-CxPAs (10/11) and a few of Inv-CxPAs (17/78) showed benign features, such as a regular shape, a well-defined border, and enhancement of posterior echo, while most Inv-CxPAs (61/78) showed one or more following features: an irregular shape, an ill-defined border, and lack of enhancement of posterior echo.

Conclusions: Ic-CxPAs tended to exhibit benign features, whereas most Inv-CxPAs tended to exhibit one or more invasive features. US can provide strong evidence in differentiating Inv-CxPAs from Ic-CxPAs.

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Introduction

Salivary gland tumors are rare and account for approximately 3% of head and neck neoplasms.¹ In this group of heterogeneous tumors, pleomorphic adenoma (PA) is the most common tumor of the salivary gland, with an incidence of 70–80%.¹ PA, as a kind of borderline tumor, may occasionally undergo malignant transformation.² Most researchers believe that malignant PA arises from a primary or recurrent benign PA (BPA).³

The most common clinical presentation of malignant PA is carcinoma ex pleomorphic adenoma (CxPA). BPA

and CxPA have sharp distinctions in terms of surgery and survival. Pathologic assessment is considered the gold standard for making a diagnosis, but it is said that benign lesions may display atypical histologic features,⁴ such as capsular infiltration, hypercellularity, cellular atypia, necrosis, and vascular invasion, which raises suspicion for malignancy, contributing to the difficulty of diagnosis. Furthermore, the mixed tumor component may be small and overlooked, and the malignant component may be difficult to classify.⁵ Overall, patients with CxPA have a poor prognosis.

Various imaging techniques have been used for the evaluation of salivary gland tumors. Ultrasonography (US) is an ideal tool for initial assessment of salivary

Correspondence to: Xiong Ping, E-mail: xiongpxp@163.com

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The authors Ding Angang and Li Jia contributed equally to the work

glands, as it is simple to perform, uses non-ionizing radiation, and is non-invasive and easily available.⁶ In many diseases, sonography is the first-line imaging modality in the assessment of salivary glands.⁷ According to the extension of invasion beyond the capsule of the previous PA, CxPAs are classified as intracapsular (without invasion), minimally invasive (<1.5 mm of invasion) and invasive (≥1.5 mm of invasion).⁸ Herein, our study aims to describe the features of CxPA assessed via US to provide a differential diagnosis imaging method for masses of the salivary gland.

Methods and patients

Patients

In this study, the data of 87 consecutive patients (89 lesions) treated at our hospital between 2010 and 2015 were retrospectively reviewed. The data were obtained using a standard of care clinical protocol from the Department of Ultrasound, Shanghai Ninth People's Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai, P.R. China. Institutional review board approval was also obtained for the retrospective review of patients' medical data. As this was a retrospective study, written informed consent was not required.

Imaging methods

Certified sonologists performed US on patients with CxPA before surgery using the GE Voluson E8 (GE Healthcare, Zipf, Austria) and the MyLab Twice ultrasound system (Esaote, Genova, Italy). The frequency of the transducers was 10 MHz. The lesions were evaluated using the Gray scale and Doppler US, and the lesion size was recorded. US characteristics, such as shape, border, echogenicity, echo texture, posterior echo, vascularity, and regional lymph node enlargement were assessed.

Preoperative evaluation

In this study, the lesion size was represented by the maximal length of the transverse section.

The shapes of the lesions was classified as oval, lobulated, or irregular.

The border of the lesions was evaluated as well-defined or ill-defined from the surrounding normal salivary tissue.

Lesion echo was classified as hypoechoic or mixed-echoic in comparison with the surrounding normal salivary gland tissue echo pattern. No isoechoic and hyperechoic lesions were found in any of the patients.

The echo texture from US images was evaluated as homogeneous or heterogeneous. Heterogeneous lesions included cystic changes, internal calcification, and mixed-echogenicity area.

The presence of posterior echo was divided into posterior echo enhancement and lack of enhancement of posterior echo (posterior echo unchanged and posterior echo attenuation).

The regional lymph node enlargement was described as enlarged lymph nodes (10 mm) with thickening, lobulation, or both thickening and lobulation of the hypoechoic lymph node cortex compared with other ipsilateral or contralateral lymph nodes.

Vascularization was classified according to two grades. Poorly-vascularized lesions had no vessels or a few vessel segments of no more than three blood vessels visible in the whole mass via Color Doppler Flow Imaging. Well-vascularized lesions had more than three blood vessels visible in the whole mass.

Histopathological analysis

After surgical resection of the tumor, histopathological analysis was performed by two pathologists. The lesions were classified as intracapsular CxPA (without invasion, Ic-CxPA) and invasion CxPA (minimally invasive or invasive, Inv-CxPA) based on the extension of invasion beyond the capsule of the previous PA.

Data analysis

Statistical analysis were performed using the IBM SPSS 19.0 Statistics for Windows software (IBM Corp., Armonk, NY). One-way analysis of variance (ANOVA), nonparametric test, Fisher's exact test, Chi-square test and receiver operating characteristic (ROC) curve were utilized for the analyses of the US findings of Ic-CxPA and Inv-CxPA, with $p < 0.05$ defined for having statistical significance.

Results

All of the malignant PAs included were CxPAs. In each of the groups, there is one patient having two lesions. Of the 89 lesions, 11 Ic-CxPA lesions, and 78 Inv-CxPA lesions were identified, Ic-CxPA is rare.

Clinical findings

Relevant clinical findings such as age, sex, and lesion site were noted (Table 1).

Table 1 Clinical characteristics of benign and malignant tumors

Variables	Ic-CxPA	Inv-CxPA
<i>n</i>	10	77
Sex		
Male	8	49
Female	2	28
Age		
Average ± SD	49.1 ± 12.6	53.7 ± 15.5
Range	29–65	21–81
Region		
Parotid gland	9	64
Submandibular gland	2	14

Ic-CxPA, intracapsular carcinoma ex pleomorphic adenoma; Inv-CxPA, invasive carcinoma ex pleomorphic adenoma.

Table 2 Summary of sonographic characteristics of Ic-CxPA and Inv-CxPA lesions

Variables	Ic-CxPA	Inv-CxPA
<i>n</i>	11	78
Size $\pm$ SD (mm)	23.8 $\pm$ 6.9	27.4 $\pm$ 11.2 (<i>n</i> = 75)
Shape		
Ovoid	4	16
Lobulated	6	22
Irregular	1	40
Border		
Well-defined	11	38
Ill-defined	0	40
Echogenicity		
Hypoechoic	8	54
Mixed-echoic	3	24
Echotexture		
Homogeneous	0	0
Heterogeneous	11	78
Cystic changes		
Present	1	9
Calcification		
Present	0	21
Posterior echo		
Without enhancement	0	43
Enhancement	11	35
Vascularity		
Poorly-vascularized	5/6	33/44
Well-vascularized	1/6	11/44
Abnormal lymph nodes		
Present	0/2	13/26

Ic-CxPA, intracapsular carcinoma ex pleomorphic adenoma; Inv-CxPA, invasive carcinoma ex pleomorphic adenoma.

In the CxPA groups, a marked male predominance of 65.5% (57/87) was recorded. Furthermore, malignancy was more prevalent among older patients; the age of onset for Ic-CxPA was younger than that of Inv-CxPA (49.1 ± 12.6 y vs 53.7 ± 15.5 y), but the difference was not statistically significant (ANOVA, $p = 0.37$).

With respect to the anatomical site, we found that in Ic-CxPA and Inv-CxPA groups, the incidence of lesions was the highest in the parotid gland (81.8 and 83.1%, respectively), followed by the submandibular gland. The study found no CxPA located in the small salivary glands.

US characteristics

Table 2 summarizes the US findings. The overall accuracy of US in determining tumor site was 100%.

Three tumors in Inv-CxPA group were too large to be measured. The average ($\pm$ SD) tumor size of Ic-CxPAs and Inv-CxPAs were 23.8 ± 6.9 mm (range, 13–36 mm) and 27.4 ± 11.3 mm (range, 5–70 mm). There was no significant difference (Nonparametric test, $p = 0.297$).

Figure 1 Gray-scale ultrasound of a 52-year-old male in the right parotid gland shows a lobular, well-defined, mixed-echoic, heterogeneous mass (arrow), with acoustic enhancement. Histopathological revealed intracapsular-Carcinoma ex pleomorphic adenoma.

With regard to morphological characteristics, 10 (90.9%) Ic-CxPA lesions (Figure 1) exhibited regular (lobulated and ovoid) appearances, while 38 (48.7%) Inv-CxPA lesions had regular shapes. More than half of Inv-CxPA lesions (40, 51.3%) had irregular shape (Figure 2). There was a significant difference between Ic-CxPA, and Inv-CxPA lesions regarding tumor shape (Chi-square test, $p = 0.009$).

Figure 2 Gray-scale ultrasound of a 54-year-old male in the left parotid gland shows an irregular, ill-defined, mixed-echoic with calcification, heterogeneous mass (big arrow), without acoustic enhancement, and see abnormal lymph nodes in the submandibular region (small arrow). Histopathological revealed invasion-Carcinoma ex pleomorphic adenoma, and invasion to the nerve.

In terms of tumor border, 11 (100%) Ic-CxPA lesions had a well-defined border; while 40 (51.3%) Inv-CxPA lesions had an ill-defined border, *i.e.* all lesions with ill-defined borders were Inv-CxPA. There was a significant difference between Ic-CxPA and Inv-CxPA lesions regarding the tumor border (Fisher's exact text, $p = 0.001$).

When it comes to echogenicity, no hyperechoic or isoechoic lesions were found in any of these patients. 23 (72.7%) Ic-CxPA lesions, and 54 (69.2%) Inv-CxPA lesions were hypoechoic. No significant difference is noticed (Fisher's exact text, $p = 0.059$).

In terms of echo texture, all Ic-CxPA and Inv-CxPA lesions were heterogeneous. It is worth mentioning that Ic-CxPA, and Inv-CxPA tend to be present with very little liquid area (1/11, 9.1 *vs* 9/78, 11.5%, respectively). Ic-CxPA masses did not show calcification, and all 21 lesions with calcification were Inv-CxPA, but there was no significant difference (Fisher's exact text, $p = 0.060$).

The posterior echo was also measured. All Ic-CxPA showed an enhancement echo (100%), while more than half of Inv-CxPA lesions (43, 55%) showed no enhancement. In other words, all cases with no enhancement of the posterior echo (8 posterior echoes attenuation and 35 posterior echoes unchanged) were Inv-CxPAs. There was a significant difference between Ic-CxPA and Inv-CxPA lesions regarding posterior echo (Fisher's exact text, $p = 0.001$).

Lymph node US was carried out on only 2 patients in Ic-CxPA group and 26 patients in Inv-CxPA group. 13 cases showed regional lymph nodes enlargement in Inv-CxPA group, while the 2 patients in Ic-CxPA group showed no regional lymph nodes enlargement. There was no statistical difference between the two groups (Fisher's exact text, $p = 0.484$), which may be due to the small sample size.

Color Doppler US was performed on 6 patients in Ic-CxPA group and 44 patients in Inv-CxPA. The majority of both groups (5/6, 83.3 *vs* 33/44, 75%, respectively) showed a poor vascularization. No statistically significant difference was observed (Fisher's exact text, $p = 1.00$).

Therefore, the irregular shape, ill-defined border, lack of enhancement of posterior echo are the invasive indicators for the diagnosis of Inv-CxPA, but if these invasive indicators are analyzed separately using ROC analysis, the sensitivity is low (Table 3). We further analyzed the 89 masses, they were classified according to the number of invasive features for Inv-CxPA. In Inv-CxPA, 17 had no features, 21 had only one, 11 had two, and 21 had three features. In Ic-CxPA, only 1 had one feature, the other 10 remaining had no features. Based on ROC analysis, these subjects were classified into two groups based on the number of features: those with no invasive features and those with one or more invasive features, the sensitivity and specificity for diagnosing Inv-CxPA were 85.9 and 90.9%, respectively (Table 3).

Table 3 Efficacy of malignant features in diagnosis of Inv-CxPA

Feature	AUC	<i>p</i> value	Youden index	Sensitivity	Specificity
Irregular shape	0.771	0.024	0.422	51.3%	90.9%
Ill-defined border	0.756	0.006	0.513	51.3%	100%
Posterior echo is not enhanced	0.782	0.003	0.564	56.4%	100%
One or more features	0.918	0.000	0.768	85.9%	90.9%

AUC, area under curve; Inv-CxPA, invasive carcinoma ex pleomorphic adenoma.

Discussion

Occasionally, a PA may undergo malignant transformation, resulting in CxPA or carcinosarcoma. The symptoms of CxPA are quite similar to those of BPA.⁹ A further paradox is the rare occurrence of histologically benign-looking PAs that metastasize.¹⁰ The rate of PA malignant transformation varies in different reports. Its true frequency is difficult to determine because of the differences across studies in tumor classification, diagnostic criteria, and patient populations. Overall, the malignant transformation rate is between 1.5 and 13.8%.¹¹

Ic-CxPA and Inv-CxPA have different prognosis, and the pathogenesis is still not clear. It was reported recently that myoepithelial cells are involved in the autophagy-senescence phenotype that leads to their disappearance. This mechanism liberates the first invasion barrier for malignant cells, explaining one of the early events involved in the progression of carcinoma *in situ* to invasive carcinoma.¹²

Maahs *et al*¹³ reported that, clinically, the most common manifestation of PA is a single lesion. In our series, 2 cases had multiple masses: one case is Ic-CxPA in a 65-year-old male with two lumps appearing in the left and right parotid gland, another is a 47-year-old male with Inv-CxPA both appearing in the left parotid gland.

Studies on the imaging features of CxPA are rare. Keerthi *et al*⁵ reported a CxPA in the superficial part of the left parotid gland, wherein a preoperative CT scan showed a heterogeneous ill-defined lesion with few areas of low-density necrosis that showed heterogeneous enhancement on contrast CT. Antony *et al*⁹ indicated that MRI is deemed a superior diagnostic tool to CT, as it is most sensitive in detecting malignancy and allows better delineation of tissue planes. However, the first diagnostic imaging assessment for salivary glands tumors is usually US. A complete US assessment covers tumor sites and features of single or multiple lesions, including solid, cystic, or cyst-solidary, well- or ill-defined, and poorly or well-vascularized masses.⁶ Sodhi *et al*¹⁴ assessed the role of high resolution ultrasound in parotid lesions in children and determined that US helps to quickly differentiate parotid from non-parotid

masses, which is particularly relevant if the lesion is at the level of parotid tail, where this can pose a problem for both clinicians and radiologists. PA is thought to have some typical ultrasonic features, such as being lobulated, heterogeneous, and poorly-vascularized. Sonography is sufficient for imaging benign parotid tumors before surgery in most patients, while it is difficult when there is extension to the deep lobe or when malignancy is probable.¹⁵

In this study, we analyzed the US findings of Ic-CxPA and Inv-CxPA. The echogenicity and homogeneity of the tumors seem to have no relevance to the differential diagnosis. It is previously reported that the majority of parotid gland tumors are hypoechoic,¹⁶ and nearly half of PAs are heterogeneous,^{17,18} which is in line with our findings. We found the majority of Ic-CxPA and Inv-CxPA were hypoechoic, with a minority being mixed-echoic. No isoechoic or hyperechoic lesions were found in the present study. In addition, all of the Ic-CxPA and Inv-CxPA lesions analyzed here were heterogeneous, which may be because of the existence of necrotic and hemorrhagic areas in both tumors.¹⁹

Blood flow can be a criteria of discriminating benign and malignant tumors, as malignant tumors have rich blood flow signals.^{20,21} Nevertheless, in our research, the majority of Ic-CxPA and Inv-CxPA groups demonstrated poorly-vascularized lesions, which is in accordance with previous studies.²¹⁻²³ In this respect, blood flow seems to have no benefit to differential diagnosis.

It is known that there were significant correlations between irregular tumor shape and malignancy. We also found that more than half of Inv-CxPA lesions (51.3%) had an irregular shape, while only one (9.1%) case in Ic-CxPA group showed an irregular shape ($p = 0.009$). According to Gritzmann *et al*,²⁴ the characteristics of the border appear to be more important than shape and internal echogenicity in differentiating between benign and malignant neoplasms. In our study, we found that 51.3% of Inv-CxPA lesions had ill-defined borders, while 90.9% Ic-CxPA lesions had well-defined borders, suggesting that tumor border is an important differentiating factor. What's more, the enhancement of the posterior acoustic was also significantly related to benign tumors.²⁵ Dumitriu *et al*²⁶ assumed that the majority of PAs (87.5%) show enhancement of the posterior acoustic. Similarly, we found that all Ic-CxPAs have this enhancement, while only 44.9% (35/78) showed this phenomenon. In addition, an enlarged lymph node at the known drainage site of a salivary gland tumor site should raise the suspicion of nodal metastasis.²⁵ In this study, Ic-CxPA cases showed no calcification or regional lymph nodes enlargement, while 21 lesions with calcification and 13 lesions with regional lymph nodes enlargement in neck or parotid gland were observed in Inv-CxPA group. Although no statistical difference was detected which may be because of small sample size, calcification and enlarged lymph node should not be ignored during US examination. In terms of these findings, Ic-CxPAs

are prone to show benign features including regular shape, well-defined border and enhancement of posterior echo, while Inv-CxPAs tended to exhibit invasive features such as irregular shape, ill-defined border, and lack of enhancement of posterior echo.

To clarify the diagnostic efficacy of US for invasiveness of lesions, we performed ROC analysis. By using ROC analysis, the sensitivity for diagnosing Inv-CxPA are highest (85.9%) when having one or more invasive features (Table 3). In other words, as long as the lesion presents at least one feature in US, it is highly likely that the lesion is Inv-CxPA. The characteristics of the border and posterior echo appear to be more important in differentiating between invasive and non-invasive CxPAs. As when the features present include either ill-defined border or lack of enhancement of posterior echo, it is conclusive that the tumor examined is Inv-CxPA according to our study. For those lesions that do not present invasive features, although they are more likely to be Ic-CxPAs, the possibility of invasiveness can not be completely ruled out, and other diagnostic methods need to be combined. Thus, US can provide strong evidence in differentiating Inv-CxPAs from Ic-CxPAs.

As Ic-CxPAs show benign features on US, how to further improve ultrasound for differential diagnosis of Ic-CxPA and benign lesions is the next problem to be approached. Although the accuracy and value of fine needle aspiration cytology for the preoperative evaluation of superficial parotid masses have been established, it is still controversial and others suggest imaging procedures before surgery.²⁷ Although Klotz *et al*²⁸ proposed that contrast enhanced ultrasound seems to be a quantitative and independent method for the assessment of malignant and benign parotid gland tumors, further studies are still needed to determine the technique and assess accuracy of diagnosis in near future.

Conclusion

In conclusion, Inv-CxPA lesions of the salivary glands are more frequently associated with invasive features, *i.e.* irregular shapes, ill-defined borders, lack of posterior echo enhancement, and sometimes with calcifications, regional lymph nodes enlargement, which are important for preoperative evaluation of the surgical protocol and patient prognosis. On the contrary, Ic-CxPA lesions tended to show benign features including regular shapes, well-defined borders, and posterior echo enhancement. US can provide strong evidence in differentiating Inv-CxPAs from Ic-CxPAs.

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