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Case Report

Three Cases of Noninvasive Carcinoma ex Pleomorphic Adenoma of the Parotid Gland and a Literature Survey Focusing on their Clinicopathologic Features

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Abstract : Only 30 cases of non-invasive carcinoma ex pleomorphic adenoma have been reported in the English language literature. Here, we report on three cases of non-invasive carcinoma ex pleomorphic adenoma. Only one of the 33 patients showed recurrence or metastasis after surgery most likely as a result of benign pleomorphic adenoma. Pleomorphic adenoma with focal areas showing malignant changes should be carefully assessed by serial sectioning. The prognosis and therapeutic approach will depend on evidence of capsular invasion. HER-2/neu is a useful marker in the differential diagnosis of pleomorphic adenoma versus noninvasive carcinoma ex pleomorphic adenoma.

Key words : carcinoma ex pleomorphic adenoma, HER-2/neu, salivary gland neoplasm

Introduction

Only 30 cases of non-invasive (intra-capsular) carcinoma ex pleomorphic adenoma have been reported in the English language literature¹⁻⁵⁾. Here, we report three cases of noninvasive carcinoma ex pleomorphic adenoma and we have carried out a literature survey.

Case Reports (Table 1-1, 1-2)

Case 1

A 61-year-old man was admitted to hospital, presenting with a mass in the parotid gland. The mass was not painful and had been present for about twenty years without affecting normal facial nerve function. Computed tomography revealed a solitary, well-demarcated solid tumor without calcification, measuring 45 mm in its largest dimension in the antero-lateral aspect of the left parotid gland. Fine needle aspiration cytology revealed malignant cells, and a parotidectomy was performed for complete resection of the tumor. No nodal involvement was observed and the patient received no subsequent chemotherapy or radio-

Table 1-1 Clinicopathological features of non-invasive carcinoma ex Pleomorphic adenoma in the literature

literature	case	sex	age	Site	Duration	TNM/stage	Size(diameter in mm)
Brandwein [2]	1	F	41	Parotid gland	2 months	T1N0M0	17
	2	M	64	Submandibular gland	Unknown	T2N0M0	28
	3	M	44	UN	18 months	T1N0M0	175
	4	F	65	Parotid gland	Unknown	T2N0M0	28
	5	M	34	Parotid gland	18 months	T2N0M0	23
	6	F	73	Parotid gland	10 years	T1N0M0	12
	7	M	50	Parotid gland	4 months	T1N0M0	15
	8	M	61	Parotid gland	Months	T2N0M0	35
	9	F	74	Submandibular gland	Months	T1N0M0	8
	10	F	35	Submandibular gland	3 months	T1N0M0	10
	11	F	69	Parotid gland	4 months	T1N0M0	20
	12	F	59	Parotid gland	12 years	T1N0M0	15
Lewis [4]	13	UN	UN	UN	UN	UN	UN
	14	UN	UN	UN	UN	UN	UN
	15	UN	UN	UN	UN	UN	UN
	16	UN	UN	UN	UN	UN	UN
Felix [3]	17	F	57	Parotid gland	10 months	T3N1M0	40
Di palma [7]	18	M	50	Parapharyngeal region	5 years	T2aN0M0	65
	19	F	56	Parotid gland	unknown	T1aN0M0	20
	20	M	44	Parotid gland	10 years	T2aN0M0	35
	21	F	72	Parotid gland	unknown	T2aN0M0	22
	22	M	68	Parotid gland	unknown	T2aN0M0	40
	23	F	69	Submandibular gland	2 years	T2aN0M0	25
	24	F	54	Parotid gland	unknown	T1aN0M0	40
	25	M	75	Parotid gland	unknown	T2aN0M0	25
	26	M	73	Parotid gland	unknown	T2aN0M0	15
	27	M	54	Parotid gland	unknown	T1aN0M0	19
	28	M	71	Parotid gland	42 years	T1aN0M0	30
Ethunandan [1]	29	F	59	Parotid gland	unknown	T2N0Mo	25
	30	M	77	Parotid gland	5 months	T1N0M0	20
Present cases	31	M	61	Parotid gland	20 years	T2N0M0	25
	32	M	62	Parotid gland	4 years	T2N0M0	35
	33	M	57	Parotid gland	many years	T2N0M0	40

CXPA : carcinoma ex PA
 PA : pleomorphic adenoma
 UN : unknown

NED : no evidence of disease
 PND : partial neck dissection
 TP : total parotidectomy
 PP : profunda parotidectomy

SMGE : Sub-mandibular gland excision
 SP : Superficial conservative parotidectomy
 RD : radial parotidectomy
 CP : conservative parotidectomy

therapy. The patient was monitored and remained well and without evidence of disease for 70 months after the surgery.

Case 2

A 72-year-old man was admitted to hospital, presenting with a non-painful mass in the

Table 1-2 Clinicopathological features of non-invasive carcinoma ex pleomorphic adenoma in the literature

literature	case	Treatment	Clinical outcome	Histological component	Follow-up period	HER-2/neu
Brandwein [2]	1	UN	NED	UN	5 years	UN
	2	UN	NED	UN	3 years	UN
	3	UN	NED	UN	3 years	UN
	4	UN	NED	UN	13 years	UN
	5	UN	NED	UN	9 years	UN
	6	UN	NED	UN	4 years	UN
	7	UN	NED	UN	4 years	UN
	8	UN	NED	UN	3 years	UN
	9	UN	NED	UN	3 years	UN
	10	UN	NED	UN	12 years	UN
	11	UN	NED	UN	1 year	UN
	12	UN	NED	UN	1 year	UN
Lewis [4]	13	UN	NED	adenocarcinoma NOS	UN	UN
	14	UN	NED	adenocarcinoma NOS	UN	UN
	15	UN	NED	adenocarcinoma NOS	UN	UN
	16	UN	NED	salivary duct carcinoma	UN	UN
Felix [3]	17	TP + cervical lymphadenectomy + radiotherapy 50Gy	NED	high grade adenocarcinoma	36 months	UN
Di palma [7]	18	RP	NED	UN	12 months	UN
	19	SP	NED	low grade spindle cell myoepithelial CXPA	12 months	1
	20	SP	NED	UN	24 months	3
	21	SP	NED	UN	3 years	2
	22	SP	NED	high grade spindle cell myoepithelial CXPA	3 years	0
	23	Resection	NED	UN	6 years	3
	24	SP	NED	UN	1 years	3
	25	SP + PND	NED	UN	1 years	3
	26	CP	NED	UN	2 years	2
	27	CP	NED	UN	2 years	3
	28	CP	NED	UN	2 years	3
Ethunandan [1]	29	SMGE	NED	UN	15 months	UN
	30	SP	NED	salivary duct carcinoma	36 months	UN
Present cases	31	SP	NED	adenocarcinoma NOS	5 years 10 months	2
	32	PP	NED	adenocarcinoma NOS	3 years 1 month	2
	33	SP	NED	adenocarcinoma NOS	36 months	2

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parotid gland, which had been present for four years and with normal facial nerve function. Computed tomography revealed a well-demarcated solid tumor without calcification, measuring 30 mm in its largest dimension in the lateral aspect of the right parotid gland. Magnetic resonance imaging revealed capsular invasion but fine needle aspiration cytology did not reveal malignant cells. A clinical diagnosis of pleomorphic adenoma was made. Profunda parotidectomy was performed. No nodal involvement was observed and the patient received no subsequent chemotherapy or radiotherapy. The patient was monitored and remained well and without evidence of disease for 37 months after the surgery.

Case 3

A 57-year-old man was admitted to hospital, presenting with a non-painful mass of the parotid gland that was present for many years with normal facial nerve function. Computed tomography revealed a solitary, well-demarcated solid tumor without calcification, measuring 25 mm in its largest dimension in the inferior aspect of the left parotid gland. A clinical diagnosis of pleomorphic adenoma of the parotid gland was made. Superficial parotidectomy was performed and no nodal involvement observed. The patient received no chemotherapy or radiotherapy and was well without evidence of the disease 36 months after the surgery.

Histopathological findings (Figs. 1, 2, 3)

The resected parotid tissues were 70×45×15 mm in Case 1, 35×30×22 mm in Case 2, and 40×35×20 mm in Case 3. Histological analysis of sections of the resected tissues revealed well-demarcated nodular tumors, measuring 25 mm in Case 1 (Fig. 1-A), 35 mm in Case 2 (Fig. 2-A), and 25 mm in Case 3 (Fig. 3-A). All three tumors were solid, hard and myxomatous and appeared grayish-white without necrotic foci or hemorrhage. Microscopic observation of the tumors showed well-circumscribed pleomorphic adenoma surrounded by a fibrous capsule, which was not invaded by the tumor (Figs. 1-B, 2-B, 3-B). In addition to the presence of definite benign areas, there was a diffuse area showing carcinomatous changes occupying 30% in Case 1, 20% in Case 2, and 50% in Case 3. These changes included cells exhibiting an eosinophilic cytoplasm, atypical nuclei, prominent nucleoli (Figs. 1-C, 2-C, 3-C), and mitosis. These features were similar to those of an adenocarcinoma not otherwise specified. Malignant tubules and benign ducts, which were associated with benign-looking myoepithelial cells, showed transitional features. There was no evidence of vascular or perineural invasion, and careful examination of serial sections of the entire capsule revealed that the tumors were confined by capsular tissue. There was no nodal involvement and the tumors were diagnosed as noninvasive carcinoma ex pleomorphic adenoma. Immunohistochemical analysis for HER-2/neu showed that carcinoma foci were moderately positive, but adenoma foci were completely negative (Figs. 1-D, 2-D, 3-D).

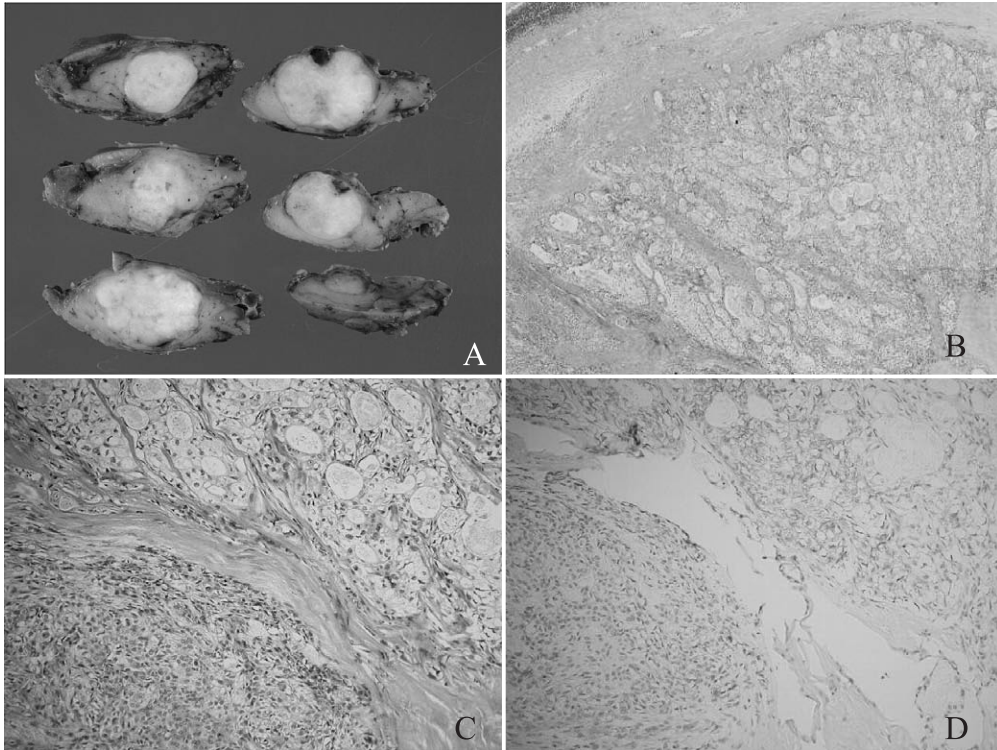


Fig. 1. Histopathologic findings of Case 1

- A: Upon sectioning, the tumor was found to be solid, hard, and white without necrotic foci or hemorrhage
- B: The tumor is surrounded by a fibrous capsule, and there is no evidence of capsular invasion. (original magnification $\times 1.25$)
- C: Adenocarcinoma is noted on the right side of the field, and pleomorphic adenoma is noted on the left side of the field. (original magnification $\times 20$)
- D: HER-2/neu expression is observed in adenocarcinoma (right side of the field), and is not observed in adenoma (left side of the field). (original magnification $\times 20$)

Discussion

Pleomorphic adenoma is the most common salivary gland neoplasm; it infrequently undergoes malignant transformation. The propensity for malignant transformation by either clinical or histological criteria is 1.9–23.3% and carcinoma ex pleomorphic adenoma represents approximately 12% of all malignant salivary gland tumors^{4,5}. Although the ratio of malignant transformation is unclear in the salivary gland tumors we have examined in the last 10 years, we identified 155 pleomorphic adenomas and 15 carcinoma ex pleomorphic adenomas. Carcinoma ex pleomorphic adenomas are generally divided into three histopathological types: noninvasive, minimally invasive (less than 1.5 mm of invasion beyond the lesional capsule), and invasive type⁶. In our 15 cases of carcinoma ex pleomorphic adenoma, three cases of noninvasive type, no case of minimally invasive type, and 12 cases

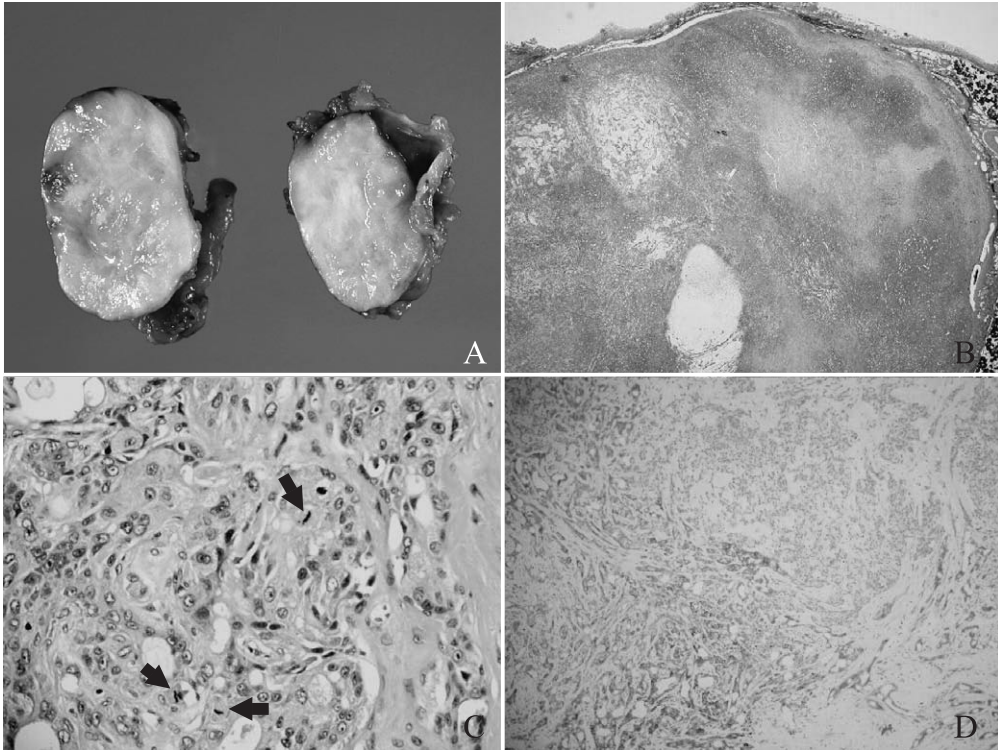


Fig. 2. Histopathologic findings of case 2

- A: On sectioning, the tumor is solid, hard, myxomatous and it appears citrine without necrotic foci or hemorrhage.
- B: The tumor is surrounded by a fibrous capsule, and there is no evidence of capsular invasion. (original magnification $\times 1.25$)
- C: Adenocarcinoma is seen, and some mitotic figures are observed (arrows). (original magnification $\times 20$)
- D: HER-2/neu expression is observed in adenocarcinoma (left side of the field), and is not observed in adenoma (right side of the field). (original magnification $\times 20$)

of invasive type were included.

Thirty cases of noninvasive (intracapsular) carcinoma ex pleomorphic adenoma have been reported previously but the features of four of those cases were not reported in detail^{2-5, 7, 8)}. We compared the clinical pathologic features of 30 cases previously reported with the three cases reported here (Table 1-1, 2). Of the cases with known gender, these represented 16 males and 13 females, with a mean age of 59.6 years (range, 34-77). The duration between tumor discovery and surgery ranged from two months to many years. Two of the female patients had prior irradiation directed at the head. Twenty-three tumors involved the parotid gland, four tumors involved the submandibular gland, and one tumor involved the parapharyngeal region. In the remaining cases, the regions affected by the tumor were not documented. The diameter of the tumors ranged from 8 mm to 40 mm (mean, 25.8 mm).

The method of treatment included: superficial conservative parotidectomy in eight cases,

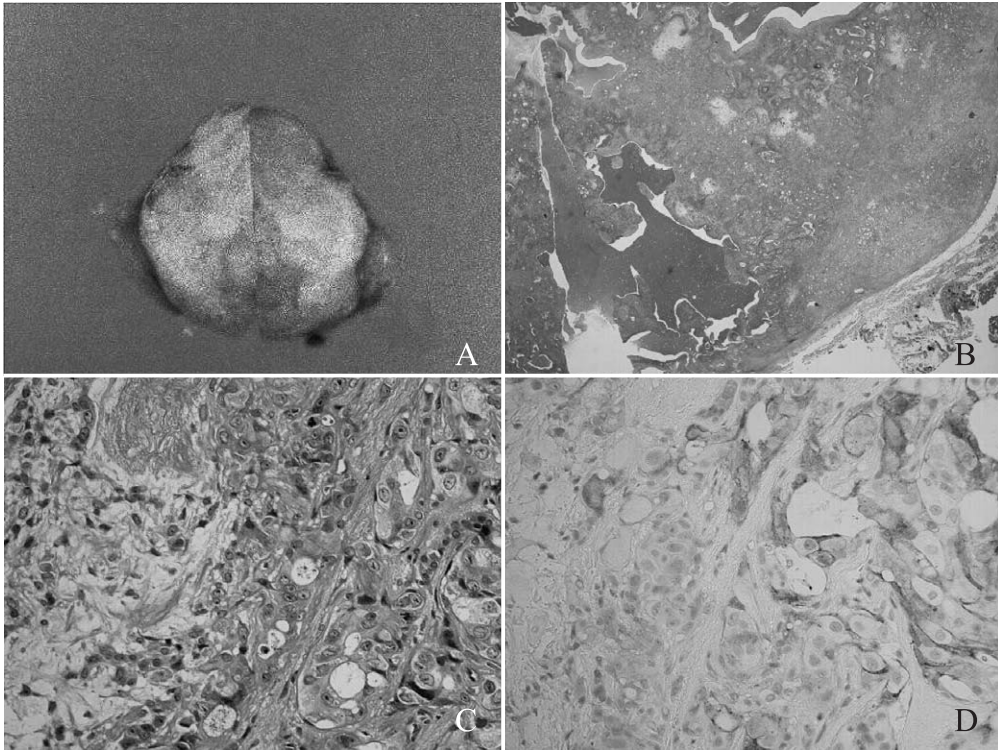


Fig. 3. Histopathologic findings of case 3

- A: Upon sectioning, the tumor was found to be solid, hard, myxomatous, and it appears grayish-white without necrotic foci or hemorrhage.
- B: The tumor is surrounded by a fibrous capsule and there is no evidence of capsular invasion. (original magnification $\times 1.25$)
- C: Adenocarcinoma is noted on the right side of the field, and pleomorphic adenoma is noted on the left side of the field. (original magnification $\times 20$)
- D: HER-2/neu expression is observed in adenocarcinoma (right side of the field), and is not observed in adenoma (left side of the field). (original magnification $\times 20$)

conservative parotidectomy in three cases, sub-mandibular gland excision in one case, superficial conservative parotidectomy and partial neck dissection in one case, total parotidectomy and cervical lymphadenectomy in one case, and profunda parotidectomy in one case. The treatments in other 14 cases were not documented. The follow-up periods ranged from 4 months to 13 years (mean range, 38.6 months). Only one of the 33 patients showed recurrence or metastasis after surgery most likely as a result of benign pleomorphic adenoma³).

HER-2/neu expression, which is a marker of malignant salivary gland tumors, was examined in a total of 14 cases, including 11 previous cases and the three cases reported in this study. Twelve cases were positive for HER-2/neu and the two negative cases were non-invasive myoepithelial carcinoma ex pleomorphic adenoma cases arising in myoepithelial cells.

We conclude that pleomorphic adenoma with focal areas showing malignant changes

should be carefully assessed by serial sectioning to obtain evidence of capsular invasion, which agrees with previous reports^{2,5)}. The prognosis and therapeutic approach depend on the evidence of capsular invasion. HER-2/neu is a useful marker in the differential diagnosis of pleomorphic adenoma versus noninvasive carcinoma ex pleomorphic adenoma. This is especially true when there is a suspicion that the pleomorphic adenoma includes a malignant component or shows malignant transformation⁷⁾. Recent studies have revealed that the androgen receptor (AR), Ki-67, and p53 may also be useful markers for this differential diagnosis, although they were not examined in this study.

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