Central Mucoepidermoid Carcinoma: A Clinicopathologic and Immunohistochemical Study of 39 Chinese Patients

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Abstract: Central mucoepidermoid carcinoma (MEC) is a rare neoplasm arising intraosseously in the jaws. To clarify the clinicopathologic profile and pathogenesis of central MEC, clinicopathologic findings and follow-up data of 39 cases were collected and analyzed. There were 16 male and 23 female patients (median age, 43 y). Sixteen cases affected the maxilla, and 23 occurred in the mandible. Radiographically, most cases (32 of 39) showed a unilocular or multilocular radiolucency with bone destruction, and 7 were found with scattered calcification. The margins of the lesions were ill defined or diffused in 14 cases and relatively well defined in 25 cases. Most cases (26 of 39) were classified as low-grade MECs, whereas 13 were moderate-to-high grade. Follow-up data were available for 35 patients with a median period of 36 months. All cases were found to be primary; local recurrence occurred in 8 cases, most (75.0%) of which were low-grade tumors. Four cases showed regional lymph node metastasis, and 1 developed distant metastasis. Of 11 cases with a clinical history of the jaw cyst, 8 initially showed a typical odontogenic cyst with local MEC-like proliferation. In summary, the most likely pathogenesis of central MEC is neoplastic transformation of the epithelial lining of an odontogenic cyst, diagnosis of which should be based on clinical, radiographic, and histopathologic findings. The immunohistochemical profile of keratins is helpful in differential diagnosis. Radical surgery is the treatment of choice, whereas the role of radiotherapy or chemotherapy is still controversial, and careful long-term follow-up is necessary.

Key Words: central mucoepidermoid carcinoma, clinicopathologic profile, pathogenesis, immunohistochemistry

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Mucoepidermoid carcinoma (MEC) is the most common primary salivary gland malignancy that usually occurs in major glands. Central MEC, an intraosseous variant occurring in the jaws, is very rare, representing only 2% to 4% of all MECs.[2,12] Central MEC was first described by Lepp[19] in 1939 in the mandible of a 66-year-old woman. Owing to its rarity, the pathogenesis, biological behavior, treatment choice, and prognosis of central MEC are still controversial. Several theories regarding its origin have been postulated, such as: (1) neoplastic transformation of the epithelial lining of odontogenic cysts, (2) neoplastic transformation of the lining of the maxillary sinus, and (3) that arising from entrapped salivary gland tissues within the jaws.[4,9,17,24,26] However, none of these possibilities is universally accepted. To ascertain the clinicopathologic profile, pathogenesis, and prognosis of central MEC, we present 39 Chinese patients with central MEC.

MATERIALS AND METHODS

A total of 39 cases of central MEC were reviewed from the files of Peking University School and Hospital of Stomatology (20 cases) and from Wuhan University School and Hospital of Stomatology (19 cases) from 1985 to 2010. The criteria for selecting the present series were made in accordance with those of a few previous studies,[1,5,6] including: radiographic evidence of an osteolytic lesion, exclusion of a metastasis or the origin from a soft tissue salivary gland, and histologic confirmation. Eight cases of glandular odontogenic cysts (GOC) and 6 cases of MECs arising from salivary glands were used for comparative immunohistochemical studies.

Clinical data and gross features were collected from surgical and pathology records. Follow-up information was obtained by clinical interviews or by reviewing the medical records of the patients. SPSS 16.0 software was used to perform statistical analysis and create diagrams. Survival and disease-free survival rates were calculated using the Kaplan-Meier method. Potential prognostic factors were identified by univariate analysis using the log-rank test. Differences at $P < 0.05$ were considered significant.

Standard hematoxylin and eosin-stained slides from all cases were reviewed to confirm diagnosis, and Periodic acid-Schiff and mucicarmine-stained slides were used when necessary. Paraffin-embedded tumor tissues were available in all cases. Four-micrometer-thick serial sections were cut, and immunohistochemical staining was performed using a standard streptacidin-biotin-peroxidase complex method (LAB-SA kits, Zymed Laboratories, South San Francisco). Details of the primary antibodies used are listed in Table 1.

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TABLE 1. Antibodies Used for Immunohistochemistry

Antibody	Company	Clone	Pretreatment	Dilution
CK 7	Zymed, Carlsbad, CA	OV-TL12/30	Citrate HIER	Ready to use
CK 10/13	Zymed, Carlsbad, CA	DEK-13	Citrate HIER	Ready to use
CK 8/18	Zymed, Carlsbad, CA	Zym5.2	Citrate HIER	Ready to use
CK 14	Zymed, Carlsbad, CA	EP61	Citrate HIER	Ready to use
CK 19	Zymed, Carlsbad, CA	A53B	Trypsin (20′)	Ready to use

RESULTS

Clinical Features

The clinical data for the 39 identified central MEC cases are summarized in Table 2. The patients' ages ranged from 15 to 76 years with a median age of 43 years. There were 16 male and 23 female patients, with a male to female ratio of 1:1.4. Sixteen cases affected the maxilla, and 23 occurred in the mandible. The exact anatomic distribution of the lesion was as follows: anterior part of the jaws (3 of 39), palate (3 of 39), ramus (11 of 39), and molar region (22 of 39). Facial swelling was the commonly presenting symptom, with or without pain. Trismus, fistula, and facial numbness were seen in 6, 5, and 4 patients, respectively. The duration of symptoms ranged from 1 month to 324 months, with a median of 18 months.

Radiographically, most cases (32 of 39) showed a unilocular, lobulated, or multilocular radiolucency with bone destruction and cortical bone expansion. Seven

TABLE 2. Clinicopathologic Features of 39 Central MECs

Case	Age (y)	Sex	Site	Duration (m)	Symptom	Initial Treatment	Histo	Status (m)
1	38	M	Maxml	130	Swelling	P-maxillectomy	II	NA
2	24	M	Manml	72	Swelling	P-mandibulectomy/ND	II	NA
3	39	M	Manra	18	Swelling/pain	P-mandibulectomy/ND	I	NED/96
4	48	F	Manra	96	Swelling/pain	Curettage	I	NED/121
5	41	M	Manra	6	Swelling/pain/trismus/numb	P-mandibulectomy/ND	III	Rec/12; DOD/36
6	16	F	Manml	8	Swelling/pain	P-mandibulectomy /RA	I	Rec/30; NED/84
7	21	F	Manant	3	Swelling	segmental mandibulectomy	I	NED/60
8	40	F	Manml	276	Swelling	P-mandibulectomy	I	NED/60
9	47	M	Maxant	3	Swelling	P-maxillectomy/ND	II	NED/42
10	19	F	Manml	45	Swelling/fistula	P-mandibulectomy	I	NED/36
11	20	M	Maxml	120	Swelling	P-maxillectomy	I	NED/36
12	55	F	Manml	18	Swelling/pain/numb	P-mandibulectomy/ND	II	NED/13
13	47	M	Manra	6	Swelling	P-mandibulectomy	I	Rec/6; NED/14
14	46	F	Maxml	1	Swelling	P-mandibulectomy	II	NED/144
15	73	F	Manml	1	Swelling	Curettage	I	Rec/36; NED/120
16	43	M	Manra	216	Swelling	P-mandibulectomy	I	NED/63
17	57	F	Maxml	324	Swelling/fistula	P-mandibulectomy	II	NED/36
18	64	F	Maxml	1	Swelling/pain/trismus	P-maxillectomy/ND	II	NED/13
19	53	M	Maxml	4	Swelling/pain	P-maxillectomy	I	NED/6
20	29	M	Maxml	51	Swelling/fistula	Curettage	I	Rec/45; NED/130
21	25	M	Manra	60	Swelling/pain/trismus	P-mandibulectomy	I	NED/38
22	26	M	Maxml	18	Swelling/pain/fistula	Curettage	I	Rec/30; NED/36
23	47	F	Maxant	7	Swelling/pain/trismus	Curettage	II	Rec/4; NED/33
24	55	F	Manml	23	Swelling	Curettage	I	NED/12
25	62	M	Manra	18	Swelling	Curettage	I	NED/10
26	15	F	Maxpa	12	Swelling/pain	Curettage	I	Rec/60; NED/91
27	23	F	Maxml	120	Swelling	P-maxillectomy	I	NED/6
28	55	F	Manra	18	Swelling	P-mandibulectomy/ND	II	NED/55
29	49	F	Manra	12	Swelling	P-mandibulectomy	I	NED/60
30	46	F	Manra	240	Swelling	P-mandibulectomy	I	NED/29
31	38	F	Maxpa	12	Swelling	P-maxillectomy	I	NED/153
32	65	M	Manml	6	Swelling/pain/numb	P-mandibulectomy	III	DOD/24
33	36	F	Manra	37	Swelling/pain/trismus	P-mandibulectomy	I	NA
34	58	F	Manml	66	Swelling	P-mandibulectomy	I	NED/47
35	32	F	Maxpa	72	Swelling/pain/trismus/fistula/numb	P-maxidibulectomy/RA	II	NED/13
36	43	M	Maxml	12	Swelling/Pain	P-maxidibulectomy	III	NA
37	29	F	Maxml	4	Swelling	P-maxidibulectomy	I	NED/10
38	55	M	Manml	1	Swelling	P-maxibulectomy	I	NED/13
39	76	F	Manml	6	Swelling	P-mandibulectomy	I	NED/70

ant indicates anterior part of both jaws; DOD, dead of disease; F, female; Histo, histologic grade; M, male; Man, mandibular; Max, maxillary; ml, molar region; NA, not available; ND, neck dissection; NED, no evidence of disease; P, partial; pa, palate; RA, radiotherapy; ra, ramus; Rec, recurrence.

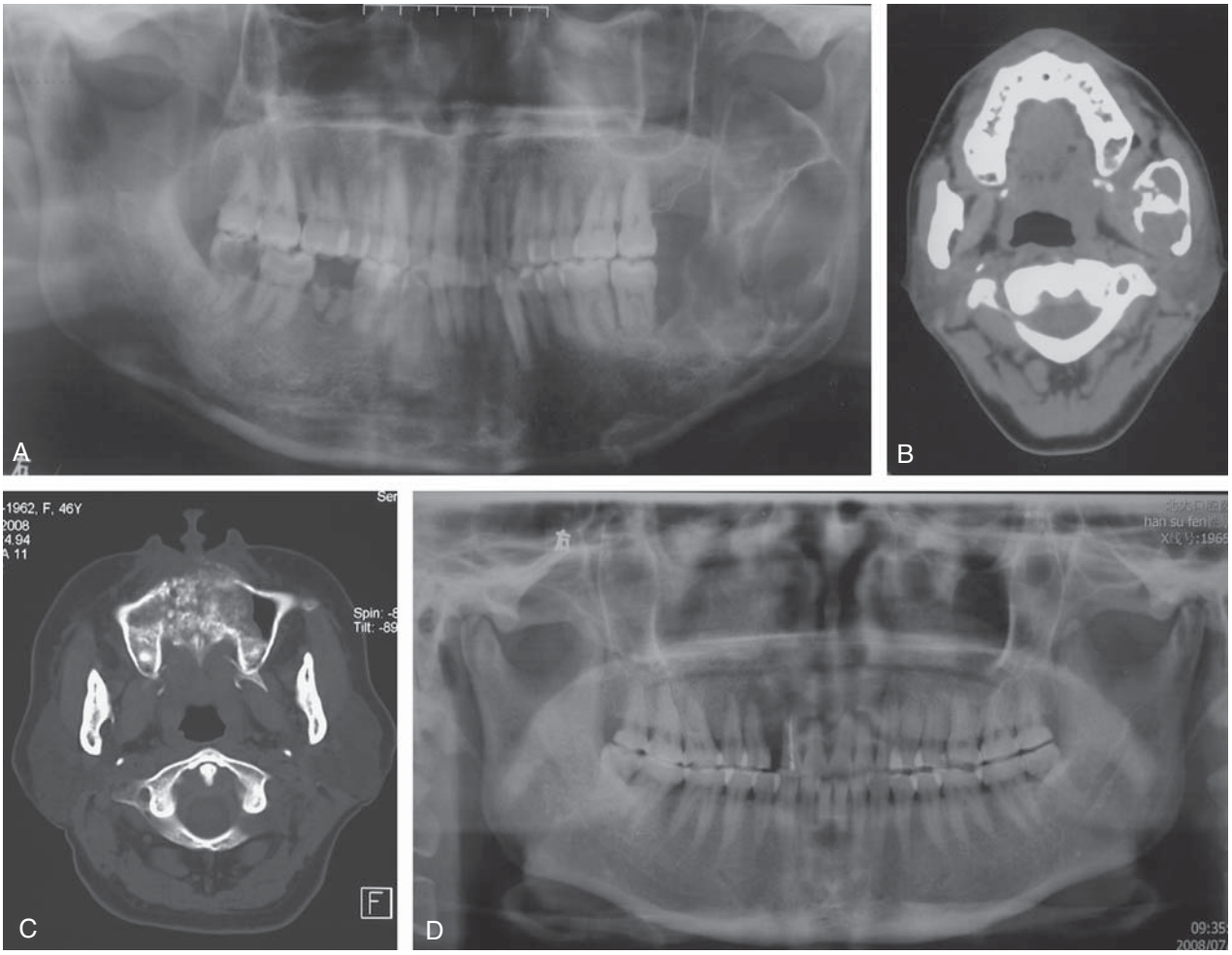

FIGURE 1. Radiographic features in central MEC. A and B, Multilocular radiolucency with relatively well-defined margin in the left mandible. C and D, Ill-defined lesion with evident bone destruction in the anterior part of the maxilla.

cases (18%) were found with scattered calcification. The margins of the lesions were ill defined or diffused in 14 cases (35.9%) and relatively well defined in 25 cases (64.1%) (Fig. 1). Five cases were found with cortical perforation. Only 3 mandibular tumors were found to be associated with an impacted wisdom tooth.

Pathologic Findings

Microscopic examination usually revealed a neoplasm composed predominantly of cystic spaces and an epidermoid component in a fibrous stroma. The cystic spaces were of varying sizes, lined by mucous-secreting cells and cells of intermediate type. Islands of squamous cells could also be seen in the area forming the epidermoid component. Most cases (25 of 39, 64.1%) were classified as low-grade MEC; 10 and 3 cases were found to be of moderate and high grade, respectively (Fig. 2).

Treatment and Follow-up

Most patients (31 of 39) were treated with segmental or total maxillectomy or mandibulectomy; 7 of them also received supraomohyoid neck dissection. Eight patients underwent curettage. Thirty patients (76.9%) were treated by surgery alone, and 2 patients received radiotherapy after surgery. Of the 11 patients with a clinical history of an odontogenic cyst (all these cysts showed clinicopathologic features of a developmental odontogenic cyst), 8 were treated by curettage initially, showing a cyst with local MEC-like proliferation. Four of these cystic lesions recurred 32, 45, 51, and 60 months after the initial treatment and were identified as central MEC after the second surgery (Fig. 3); 2 patients are alive with no evidence of disease 6 and 12 months after initial curettage (Fig. 4), and the other 2 were treated with hemimandibulectomy shortly after the initial treatment because of the massive size of the lesions and repeated swelling. These 2 patients were then confirmed as having central MEC. Another 3 cases with a clinical history of an odontogenic cyst presented with central MEC after 120, 300, and 324 months, respectively.

Follow-up data were available for 35 patients ranging from 6 months to 153 months with a median of

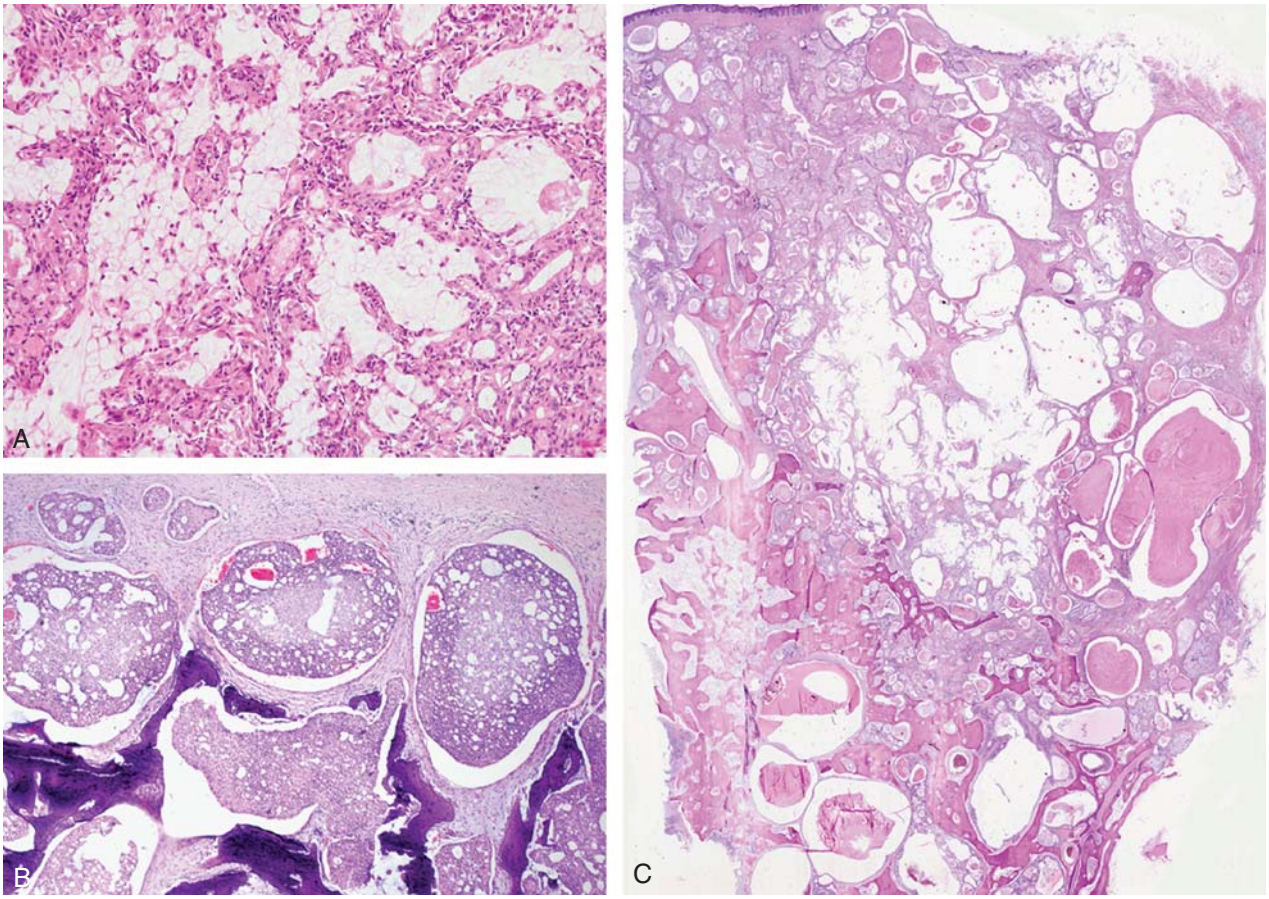

FIGURE 2. Histopathologic features in central MECs. Intraosseous tumors showing general features of MECs. A, Low-grade central MEC. B, High-grade central MEC. C, Moderate-grade central MEC.

36 months. All of the cases were found to be primary tumors, and local recurrence after initial treatment occurred in 8 cases. Four cases showed regional lymph node metastasis, and 1 patient developed distant metastasis to the lung. At the time of current analysis, 2 patients died of disease. By the Kaplan-Meier analysis, the overall survival rates were 96.0% at 2 years and 91.6% at 5 years, respectively. Univariate analysis showed that clinical features (with or without lip anesthesia; $P = 0.000$), histologic grading ($P = 0.015$), and lymph node metastasis ($P = 0.036$) were significant prognostic factors for survival. The cumulative probabilities of recurrence at 2 and 5 years were 9.1% and 35.3%, respectively. Univariate analysis showed that treatment modalities ($P = 0.005$) were significant prognostic factors for recurrence (Fig. 5 and Table 3).

Immunohistochemical Findings

All central MECs expressed cytokeratins (CKs) 7, 8, 18, and 19; 50% of the cases stained positively for CK 10/13; 37.5% showed CK 14 expression. All GOCs expressed CKs 14 and 19; 85.7% also showed CK 10/13 expression, whereas only 12.5% were found to be immunoreactive for CKs 7, 8, and 18 (Fig. 6).

DISCUSSION

Central MEC is a rare yet well-known neoplasm arising in the jaws, which can be clinically and radiologically mistaken for a cyst. Although about 130 cases have been reported to date, most of them are individual case reports with inconsistent information; moreover, there are still numerous problems with regard to the tumor's pathogenesis, treatment choice, and prognosis.[3,4,8,9,15,17,23,24,26] Herein, we present 39 Chinese patients with central MEC with a detailed analysis of clinical, radiologic, and pathologic features, together with follow-up data.

It has been reported that central MEC occurs most frequently in the fourth and fifth decade of life, with a male to female ratio of 1:1.45.[17] In the current series, patients' age (median, 43 y) and male to female ratio (1:1.4) were in general agreement with those of previous reports. Recently, in a literature review by Bottenberg,[17] a total of 100 cases of central MEC were analyzed, and the anatomic distribution of this tumor was as follows: palate 1%, ramus 3%, anterior part of both jaws 3%, molar region 83%, and 13% nonclassified. In the current series, the exact anatomic distribution was as follows: anterior part of both jaws (3 of 39, 7.7%), palate (3 of 39, 7.7%),

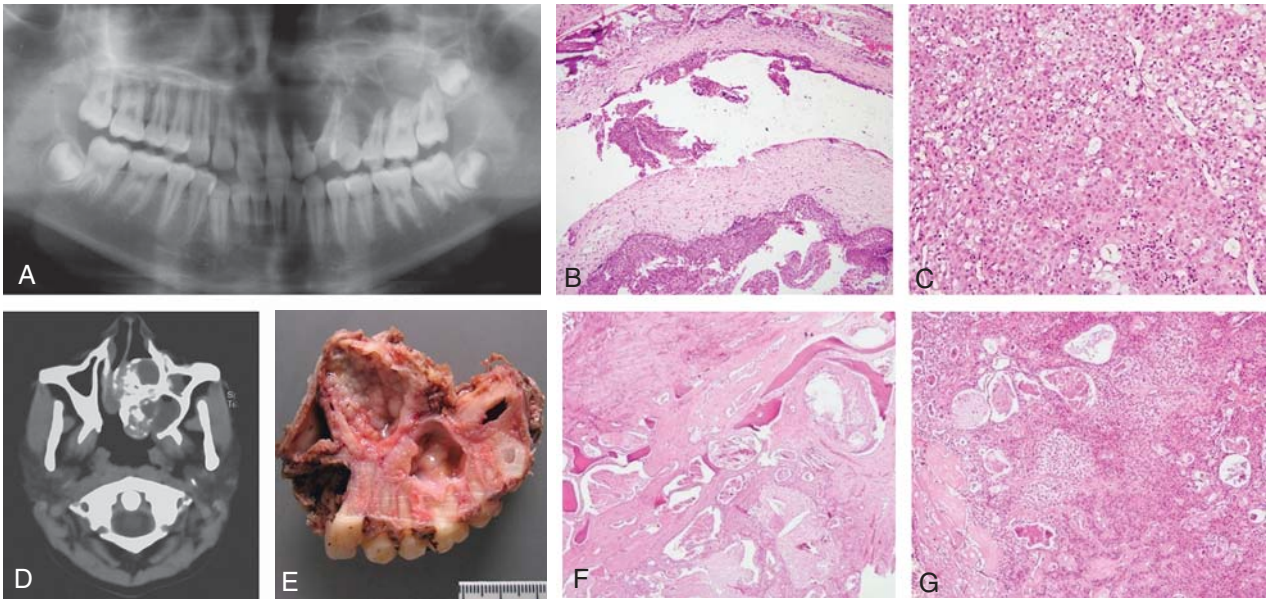

FIGURE 3. Case no. 26 with a clinical history of an odontogenic cyst. A, Radiograph showing locular radiolucency in the left maxilla. B, Low-power view of a jaw cyst with local epithelial thickening. C, High-power view of local epithelial thickening exhibiting features of MEC. D, Computed tomographic scan image showing the recurrent lesion occupying the left maxilla with bone destruction in the local area. E, The operative specimen after the second surgery showing an intraosseous solid and cystic tumor. F and G, The recurrent tumor showing histopathologic features of a typical central MEC.

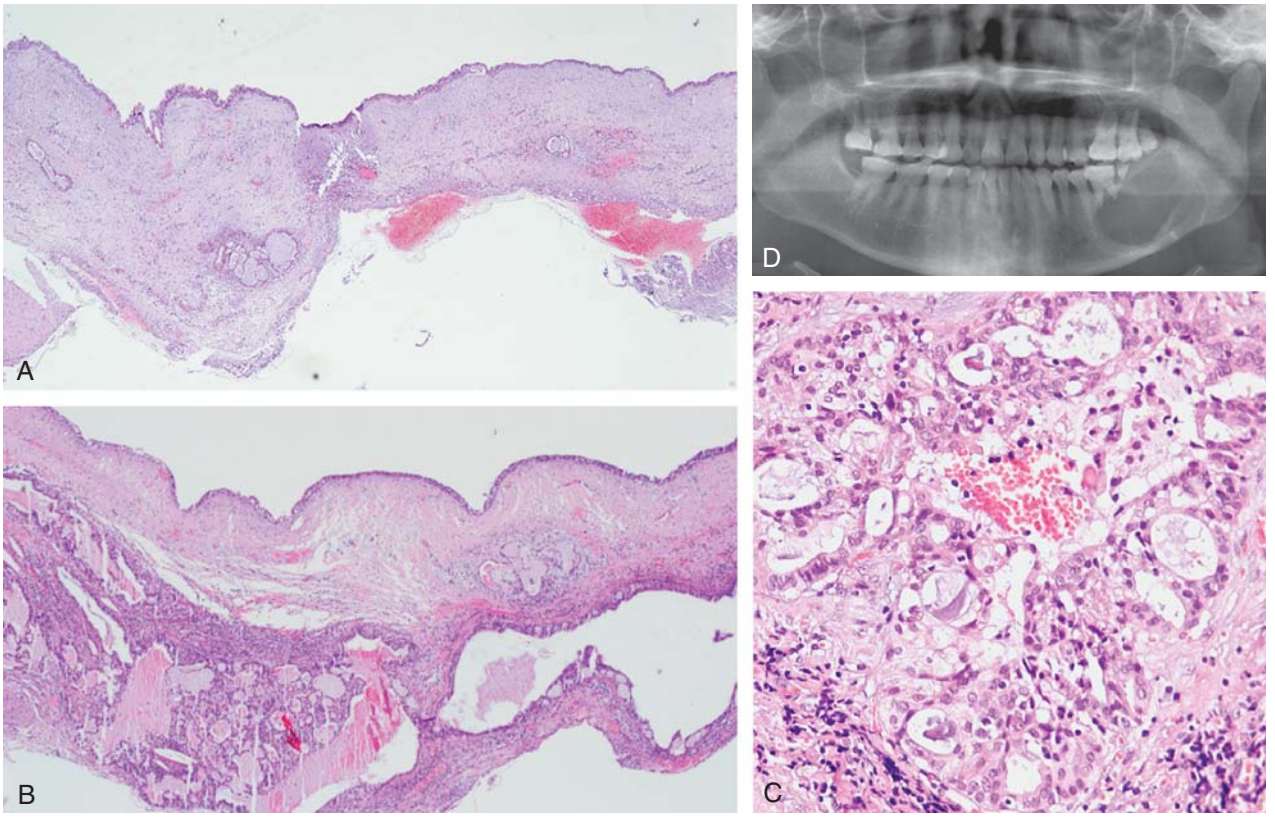

FIGURE 4. A and B, Jaw cyst with local MEC-like proliferation showing early MEC transformation in case no. 24. C, High-power view showing cystic spaces and epidermoid components composed of mucous-secreting cells, squamous cells, and cells of intermediate type. D, Radiograph showing well-defined unilocular radiolucency in the left mandible.

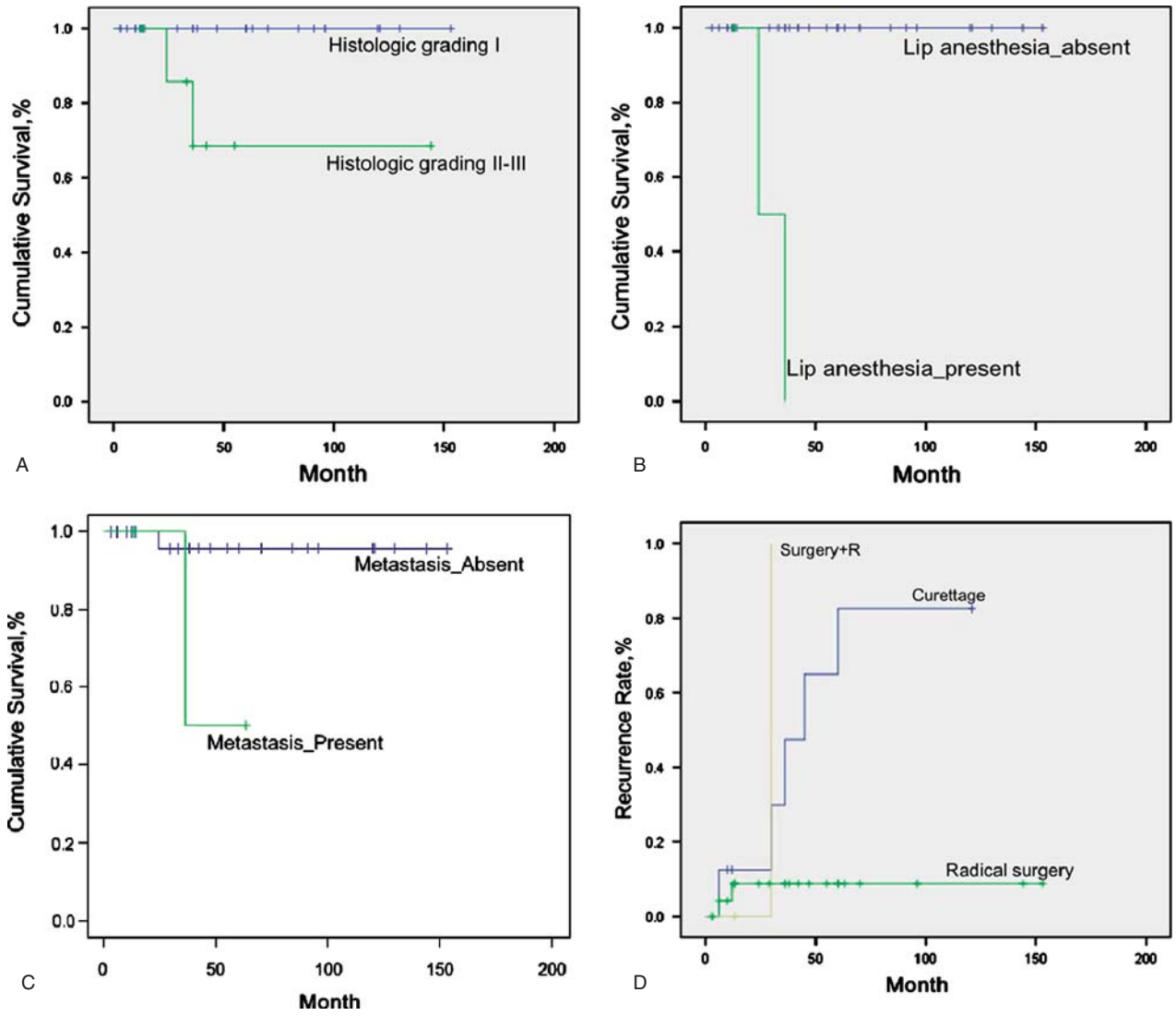

FIGURE 5. Plot of cumulative survival and recurrence rate. A, Survival based on different histologic grading of the tumors. B, Survival based on the presence or absence of lip anesthesia. C, Survival based on the presence or absense of regional lymph node metastasis. D, Recurrence rate for patients with central mucoepidermoid carcinomas undergoing different treatment modalities (curettage, radical surgery, or surgery and radiotherapy).

ramus (11 of 39, 28.2%), and molar region (22 of 39, 56.4%).

There is no definitive theory about the pathogenesis of central MEC. Several speculations have been described, including: (1) mucous metaplasia and neoplastic transformation of the epithelial lining of an odontogenic cyst; (2) entrapment of the submandibular, sublingual, or retromolar mucous glands during embryonic development within the mandible, which subsequently undergo neoplastic transformation; (3) iatrogenic entrapment of minor salivary glands; (4) neoplastic transformation of maxillary sinus epithelium; and (5) remnants of the dental lamina.[4,9,17,20,23] The most likely source of central MEC is the neoplastic transformation of the epithelial lining of an odontogenic cyst, as mucus-producing cells are commonly found in odontogenic cyst linings. Furthermore, the posterior region of the jaws is the most frequent location for both odontogenic cyst and central MEC. Eversole, in his review of the literature in 1970, found that 48% of central MECs were associated with dental cysts or impacted teeth,[10] whereas Brookstone and Huvos[5] reviewed the literature in 1992 and reported the number closer to 32%. In the current series, there were 11 cases (28.2%) of central MEC with a clear history of an odontogenic cyst in the same location, of which 7 were maxillary tumor. Interestingly, of these 11 cases, 8 presented as a typical odontogenic cyst with local epithelial thickening exhibiting features of MECs. All these cases were treated with curettage. Six of these patients were identified as having central MEC 1, 4, 32, 45, 51, and 60 months after the initial treatment, and the other 2 patients were alive with no evidence of disease 6

TABLE 3. Univariate Analysis of Survival and Recurrence of the Present Series

		Survival			Recurrence		
Variables	**No. Cases**	**2 y, %**	**5 y, %**	**Univariate *P***	**2 y, %**	**5 y, %**	**Univariate *P***
Age, y				0.874			0.581
< 45	16	100.0	92.3		7.1	44.7	
≥ 45	19	91.7	91.7		11.1	21.0	
Sex				0.060			0.231
Men	13	88.9	77.8		17.5	52.9	
Women	22	100.0	100.0		4.5	28.4	
Duration				0.244			0.121
< 36	23	93.3	86.2		14.1	44.8	
≥ 36	12	100.0	100.0		0.0	20.0	
Lip anesthesia				0.000			0.268
Absent	31	100.0	100.0		6.7	33.5	
Present	4	50.0	0.0		25.0	25.0	
Histologic grading				0.015			0.822
Grade 1	25	100.0	100.0		4.2	36.2	
Grade2 and 3	10	85.7	68.6		20.0	20.0	
Metastasis				0.036			0.593
Absent	32	95.7	95.7		6.5	35.2	
Present	3	100.0	100.0		33.3	33.3	
Treatment				0.683			0.005
Curettage	8	100.0	100.0		12.5	82.5	
Radical surgery	25	94.4	88.5		8.7	8.7	
Surgery + R	2	100.0	100.0		0.0	100.0	
Site 1				0.287			0.389
Maxillary	14	100.0	100.0		7.7	59.6	
Mandibular	21	93.8	87.1		9.8	23.7	
Site 2				0.627			0.724
Anterior	3	100.0	100.0		33.3	33.3	
Posterior	32	95.5	90.7		6.8	36.1	

Grade 1, well-differentiated central mucoepidermoid carcinoma (CMEC); Grades 2 and 3, moderately and poorly differentiated CMEC; R, radiotherapy; Anterior, the anterior region of both jaws (between the right and left canines); Posterior, the posterior region of both jaws (distal to the canines).

and 12 months after the first treatment. The other 3 cases with histologic evidence of an odontogenic cyst with no apparent local epithelial hyperplasia presented with a central MEC 120, 300, and 324 months later, respectively. These cases with direct evidence of association with a preexisting odontogenic cyst support the hypothesis that mucous metaplasia and neoplastic transformation of the odontogenic cyst could be the pathogenesis of central MEC. A jaw cyst with local MEC-like proliferation should alert the possibility of early MEC transformation, as 6 of 8 such cases in our series had shown features of typical central MEC in their recurrences.

The histologic features of central MEC are often indistinguishable from MECs arising from soft tissue salivary glands. Thus, diagnosis of central MEC is based not only on histologic features but also on clinical and radiographic parameters. The radiographic examination usually reveals a well-defined unilocular, lobulated, or multilocular radiolucency; rarely has a mixed radiolucent-radiopaque expression also been reported.[16] Tooth displacement and cortical perforation could also be found sometimes, especially in long-standing cases, and computed tomographic scans were considered to be helpful and necessary for determining the presence of bone destruction. Inagaki et al[14] classified the radiographic findings into the following 3 types: cystic, characterized by a large, cystic radiolucent area; rarefying, characterized by rarefying changes of the trabeculae; and infiltrative, characterized by a central ill-defined area of bony destruction. In the present series, osteolytic lesion was observed in all cases. Cystic radiolucency was found in 32 cases (82.1%), of which 17 were unilocular; the others were multilocular. Seven cases were found with rarefying changes of the trabeculae or with scattered calcification. The margins of the lesions were ill defined or diffused in 14 cases (35.9%) and relatively well defined in 25 cases (64.1%). Five cases were also found with cortical perforation. To establish a diagnosis of central origin, clear-cut criteria must be fulfilled. In 1974, Alexander et al[1] proposed the following criteria, which were subsequently modified by Browand and Waldron[6] and Brookstone and Huvos:[5] (1) presence of a radiographic distinct osteolytic lesion, (2) positive mucicarmine staining, (3) absence of rupture of cortical plates, (4) clinical and histologic exclusion of a metastasis or an odontogenic lesion, (5) exclusion of origin from soft tissue salivary glands, and (6) histologic confirmation. However, there are still some contradictions in the criteria. Sometimes, it is difficult to discriminate whether the neoplasm in the maxilla perforated the cortical plates or whether the tumor of surrounding soft tissues invaded the osseous tissue. This is probably the reason why the number of maxillary cases is fewer than that of mandible in previous reports. Some cases were reported to have cortical perforation, especially long-standing cases. When discontinuity of the alveolar border of the tumor occurred,

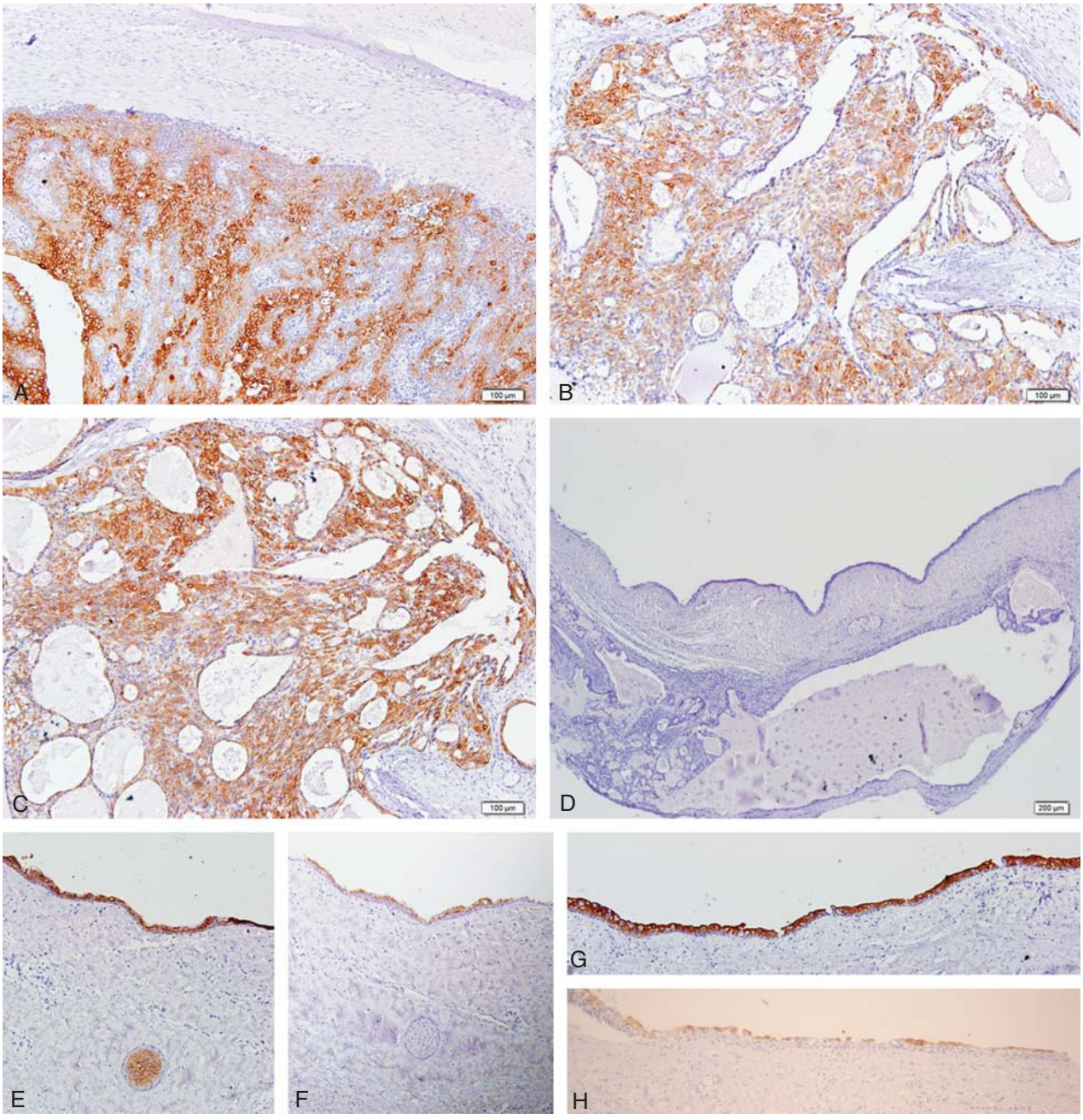

FIGURE 6. Immunohistochemical profile of keratins in central mucoepidermoid carcinoma (CMEC) and GOC. A, B, and C, Intense immunoreactivity for CKs 7, 8, and 18 in CMEC. D, Negative staining for CK 10/13 in CMEC. E and G, Strong, continuous immunoreactivity for CKs 10/13 and 19 in the whole epithelium in GOC. F and H, Weak immunoreactivity for CKs 7 and 8/18 in focal surface cells in GOC.

the diameter of the alveolar cortical perforation was essentially found to be smaller than that of the underlying tumor, which may help in differentiating intraosseous carcinomas from tumors of the soft tissue salivary glands.

As most of the cases are cystic low-grade neoplasms, central MEC should be differentiated from GOC, which may also show cystic spaces lined by epidermoid and mucoid cells. First, the presence of intermediate cells and the solid proliferation in central MEC are not seen in GOCs. Second, CK expression has been regarded as a useful tool in the identification of different epithelial types and origins. In this study, all central MECs expressed CKs 7, 8, and 18, whereas only 12.5% of GOCs stained positively for CK 7, 8, and 18, which suggests that these markers might be helpful adjunctives in differentiating central MEC from GOC.

Owing to the rarity of central MEC, the inadequacy of staging, and the disparity of treatment reported in the literature, treatment choice and prognosis evaluation are difficult to be established. It has been reported that conservative treatment such as enucleation or curettage presents a recurrence rate varying from 40% to 45%,[5,7,25] whereas radical excision has a 13% recurrence rate.[5] In this study, of the 35 cases with follow-up data, 8 cases were treated with curettage, 5 of which (62.5%) recurred, whereas only 11.1% (3 of 27) of patients treated with radical surgery were found with recurrence. Univariate analyses showed that treatment modality was a significant prognostic factor affecting recurrence, which indicated that complete resection is essential. Freje et al[11] recommend radiotherapy for high-grade tumors; an evaluation of lymph nodal status is always indicated, and neck dissection should be performed in the presence of metastases. Metastases have been reported in some cases, mainly to the regional lymph nodes, whereas lung, brain, and ipsilateral clavicle have also been reported to be involved.[5,11,13,18] In the current series, 4 cases showed regional lymph node metastasis, and 1 patient developed distant metastasis to the lung. Univariate analyses showed that regional lymph node metastasis was a significant prognostic factor for survival. It has been suggested that the histologic grade of central MEC does not appear to correlate with prognosis.[5] In this study, 26, 10, and 3 cases were classified as low, moderate, and high grade, respectively. It seems that most central MECs were of low grade (26 of 39, 66.7%). Nevertheless, even being low-grade tumors, central MECs should be treated with wide local resection or hemimandibulectomy with regard to local recurrence. However, the need for neck dissection and adjuvant treatment is still controversial, and radiotherapy seems to be an adjunctive intervention, together with close surgical margins.

In summary, the most likely pathogenesis of central MEC is neoplastic transformation of the epithelial lining of an odontogenic cyst, diagnosis of which should be based on clinical, radiographic, and histopathologic findings. Immunohistochemical profile of keratins is helpful in differential diagnosis. Radical surgery is the treatment of choice even in low-grade tumors, whereas the role of radiotherapy or chemotherapy is still controversial, and careful long-term follow-up is necessary.

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