Spindle-cell variant of ameloblastic carcinoma: a report of 3 cases and demonstration of epithelial-mesenchymal transition in tumor progression

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Ameloblastic carcinoma is a rare odontogenic neoplasm that demonstrates the histologic characteristics of ameloblastoma, accompanied by the cytologic features of malignancy. The spindle-cell variant of ameloblastic carcinoma (SCAC) is exceptionally rare, with a total of 10 cases having been reported in the literature to date. Histologically, a prominent sarcomatoid cell population appears to originate from the epithelial (ameloblastic) component. Like conventional ameloblastic carcinoma, most cases of SCAC occur in individuals older than 40 years of age. Here, 3 additional cases of SCAC are reported, 2 of which occurred in young individuals. Diagnostic criteria to aid in the identification of SCAC are proposed. Finally, histologic and immunohistochemical evidence supporting the occurrence of epithelial−mesenchymal transition in SCAC is presented. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:e113−e121)

Ameloblastic carcinoma (AC) is an uncommon epithelial odontogenic tumor that demonstrates the histologic pattern of conventional ameloblastoma, accompanied by the cytologic features of malignancy.[1,2] The definition of the term "ameloblastic carcinoma" was discussed by Shafer et al. in 1974.[3] Most AC cases seem to arise de novo, but this tumor has also been reported to arise in benign ameloblastoma.[2] AC may affect patients of any age (mean 49.2 years), and a strong sex predilection does not exist, although a few studies have reported predominance in males.[4-6] AC has a tendency to occur in the posterior mandible, and this is similar to its benign counterpart, ameloblastoma.[7] At this time, there is no consensus regarding treatment of patients with AC because of its rarity.[6] The convention is surgical resection with 2- to 3-cm margins.[2,5,6] Neck dissection, chemotherapy, and radiotherapy are of questionable value in the absence of metastasis.[8] The 5-year reported survival rate ranges from 40% to 82%, and the recurrence rate of AC is reported at 28% to 60%.[2,6]

In 1999, Slater described a "biphasic sarcomatoid carcinoma arising in conventional ameloblastoma (a variant of ameloblastic carcinoma)."[9] This has been regarded as the first description of the spindle-cell variant of ameloblastic carcinoma (SCAC), although the article was a review and no specific case information supporting a diagnosis of SCAC was reported.[9] According to Slater, SCAC is a carcinoma with proliferative areas of ameloblastoma, as well as a spindled population that resembles fibrosarcoma but lacks the histologic features of ameloblastic fibrosarcoma.[9] On the basis of this description, we derived the following histologic criteria for SCAC: (1) a carcinoma with ameloblastic differentiation; and (2) a sarcomatoid cell population, intimately associated with the epithelial component. SCAC often demonstrates a direct transition from ameloblastic islands of atypical cells to a population of spindled cells that is separate from the background stroma. The carcinomatous and sarcomatoid components are intimately associated in SCAC.[9] SCAC is quite uncommon, with only 10 cases reported in the literature.[2,7,10-17] Three additional cases of SCAC are reported here, 2 of which arose in young patients. The histomorphologic and immunohistochemical findings of these cases also support the occurrence of epithelial−mesenchymal transition (EMT) in SCAC.

METHODS

Two cases of SCAC were identified in the database of the Department of Diagnostic Sciences at the Texas A&M University College of Dentistry. An additional

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case was identified at the University of Texas Southwestern Medical Center. For each case, hematoxylin and eosin−stained slides and the results of pertinent immunohistochemistry studies were reviewed. Clinical and radiographic information was provided by the patients' referring surgeons and pathologists. A literature review was conducted on the basis of the results of a PubMed search of the English literature using the term "spindle cell ameloblastic carcinoma."

Approval from the institutional review board was deemed unnecessary for this case series.

RESULTS

Case 1

A 23-year-old white male presented to the emergency department of the Baylor University Medical Center in May 2015 with a 2-week history of swelling, pain, and loose teeth in the upper right quadrant. His medical history was noncontributory. The patient reported social alcohol use and limited cigar smoking. Clinical examination revealed a firm, expansile mass of the right posterior maxilla with mucosal ulceration (Figure 1A). The panoramic radiograph showed the right maxillary posterior teeth displaced by the mass (Figure 1B). Computed tomography (CT) images showed that the 8-cm lesion had perforated the sinus floor, occupying the right maxillary sinus and approaching the infraorbital rim (Figure 1C). A prominent submental lymph node was noted, and chest radiography revealed no evidence of lung involvement. An incisional biopsy was performed.

Microscopic examination showed a malignant odontogenic neoplasm with epithelial and sarcomatoid components. The epithelial population consisted of anastomosing islands and cords of basaloid cells, with a palisaded nuclear pattern and focal reverse polarity (Figure 2A). Transition of the carcinomatous component into a hypercellular and mildly pleomorphic sarcomatoid cell population was noted in one area (Figure 2B). Nuclear pleomorphism and infrequent mitotic figures were observed. Immunohistochemistry (IHC) for AE1/AE3 showed strong positive reactivity in the carcinoma cells, with diminished positivity in
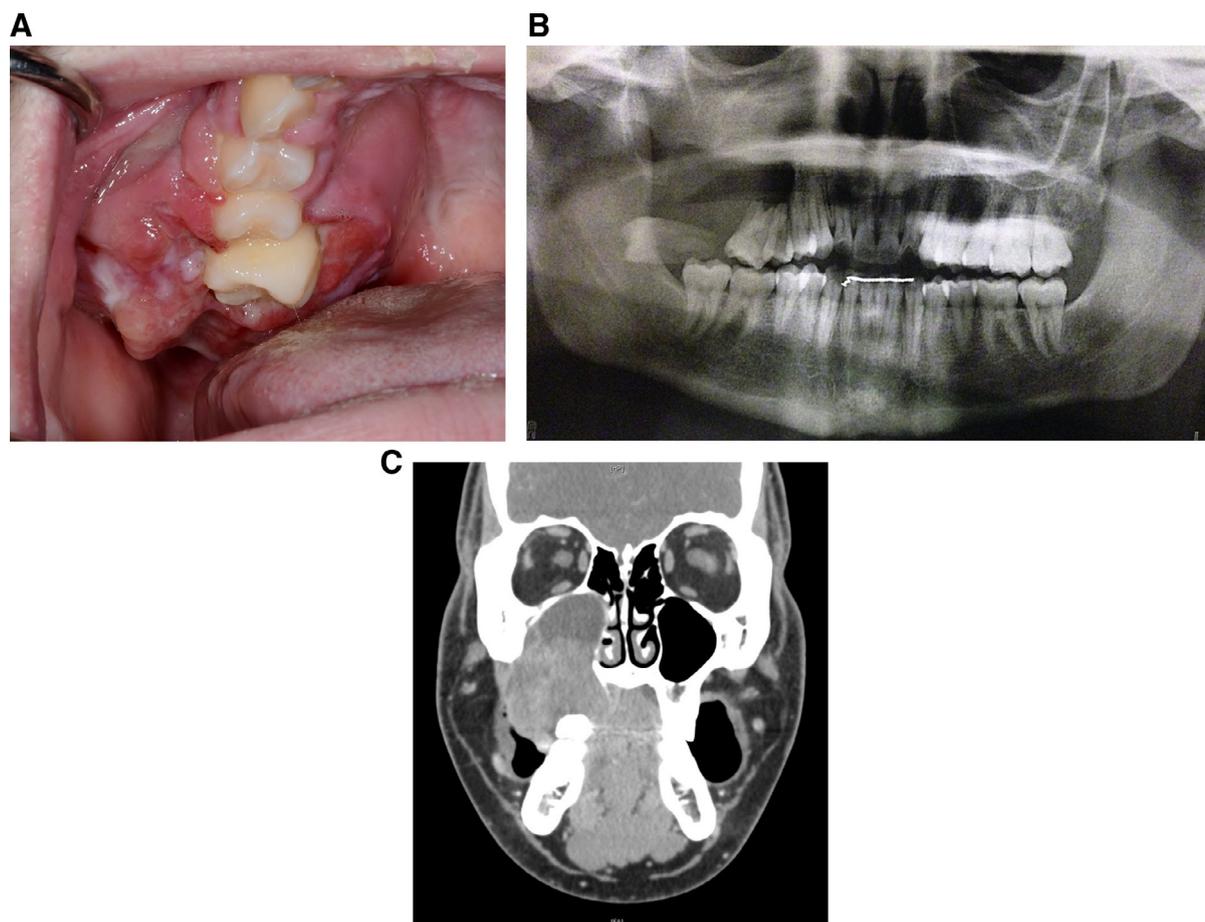

Fig. 1. Clinical presentation of case 1. **A,** The patient presented with an expansile lesion of the right maxilla with overlying ulceration. **B,** The panoramic radiograph showed a destructive radiolucency of the right maxilla, displacing teeth. **C,** A coronal view of the computed tomography (CT) image showed the 8-cm tumor had perforated the sinus floor and was approaching the infraorbital rim.
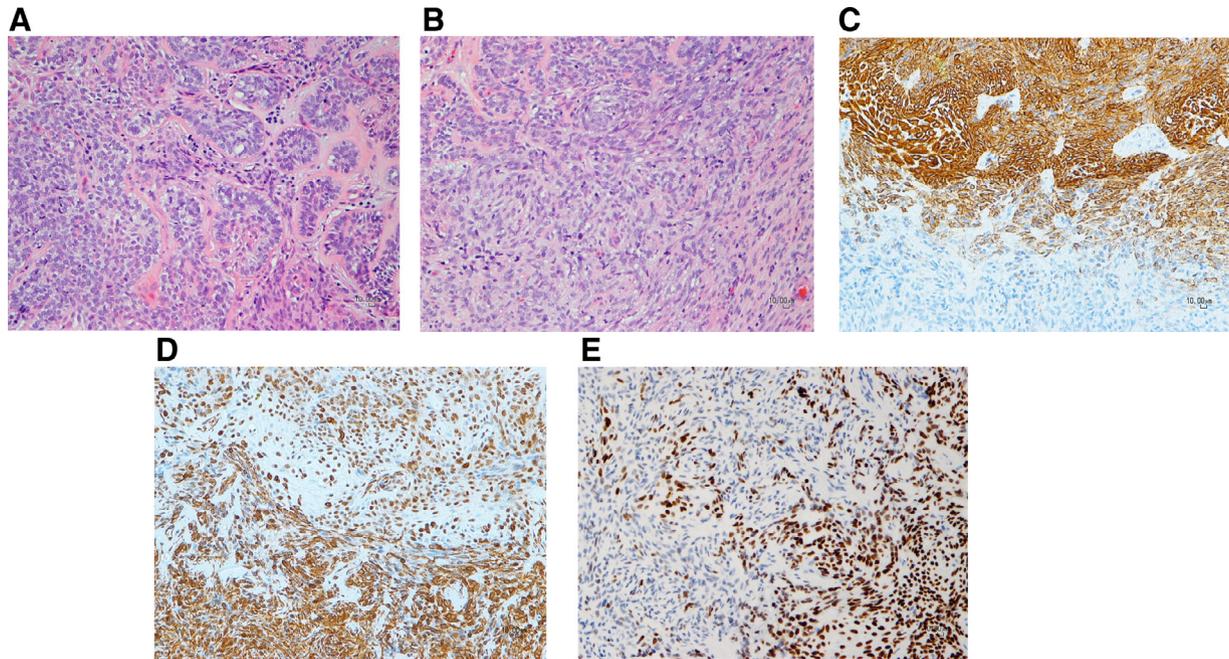
Fig. 2. Histologic features of case 1. **A,** The tumor exhibited features of ameloblastoma, including peripheral palisading and reverse polarity of tumor cell nuclei (hematoxylin and eosin [H&E], original magnification × 20). **B,** A cytomorphologic transition between the epithelial and sarcomatoid components was seen (H&E, original magnification × 20). **C,** AE1/AE3 was strongly positive in epithelial cells, and reactivity decreased in the sarcomatoid cells (original magnification × 20). **D,** Vimentin was positive in the spindle cells, and focal nuclear staining was seen in some carcinomatous cells (original magnification × 20). **E,** p40 was positive in carcinomatous cells, and scattered positivity was noted in the sarcomatoid cells (original magnification x 20). *High resolution versions of the following slides for use with the Virtual Microscope are available as eSlides:* (A) and (B) *VM05507*; (C) *VM05506*; (D) *VM05486*; (E) *VM05505.*

the sarcomatoid cells (Figure 2C). Vimentin was strongly reactive in the sarcomatoid cells, and focal nuclear expression was noted in the carcinomatous cells (Figure 2D). IHC for p40 was performed to demonstrate epithelial differentiation in the sarcomatoid component.[18] The carcinomatous cells were strongly positive for p40, whereas the sarcomatoid cells were focally positive (Figure 2E). The Ki-67 proliferative index was estimated at 6% to 10%. Cam 5.2 was positive in the epithelial cells and focally positive in the spindled cells. A diagnosis of SCAC was made on the basis of these findings.

The patient underwent a right hemimaxillectomy and unilateral selective neck dissection in May 2015. His surgical defect was reconstructed with a free fibular flap and split-thickness skin graft with microvascular anastomosis, and the patient's right eye was preserved. He received postoperative chemotherapy and radiation at Monroe Dunaway Anderson Cancer Center, and the patient's disease has not recurred at 42 months after surgery.

Case 2

A 12-year-old Hispanic female presented to the University of Texas Southwestern Medical Center with a 1-year history of a slow-growing, expansile lesion of the left posterior mandible. The patient's medical history was significant for cystic fibrosis, for which she underwent a partial lobectomy of her lung in 2013. She was taking no medications. A panoramic radiograph demonstrated a well-defined multilocular radiolucency of the left posterior mandible, extending into the ramus (Figure 3A). CT showed cortical expansion, which manifested clinically as facial asymmetry (Figure 3B). Incisional biopsy was performed, and intraoperatively, the surgeon described the lesion as a solid yet friable tumor with a yellowish appearance.

Microscopic examination of the incisional biopsy specimen revealed a cellular, sheetlike proliferation of epithelioid and spindled cells with poorly defined cell borders (Figure 4A). The surface epithelium was ulcerated, and the lamina propria was completely occupied by the neoplasm. Scattered chronic inflammatory cells and occasional mitotic figures were seen. An IHC study for AE1/AE3 showed strong positivity in the epithelioid cells (Figure 4B). As the cells transitioned to a spindled morphology, AE1/AE3 staining intensity appeared to decrease. p40 was positive in most epithelioid cells and in many of the spindled cells. Cytoplasmic expression of vimentin was noted in the
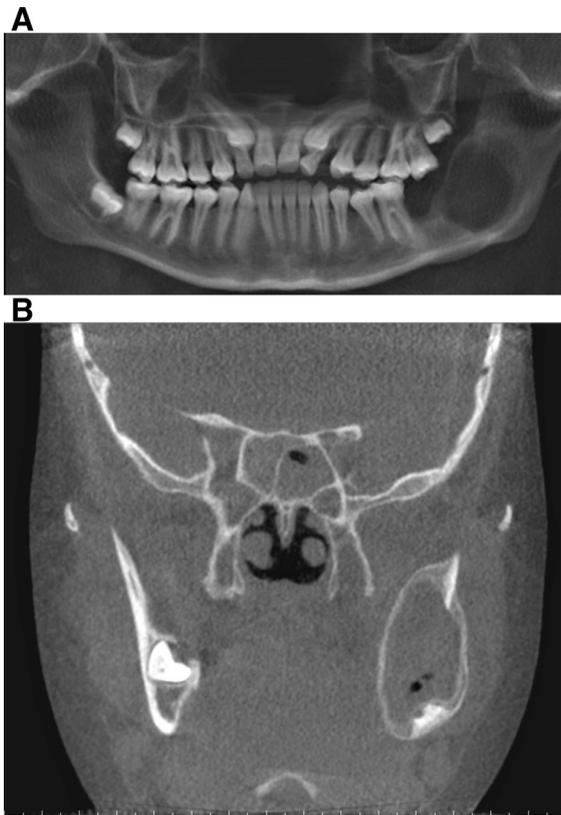
Fig. 3. Clinical presentation of case 2. **A,** The patient presented with a large radiolucency of the left posterior mandible, extending to the ramus, as seen in this reconstructed panoramic image. **B,** A coronal computed tomography (CT) image revealed an expansile lytic mandibular lesion.

spindled cells, and scattered nuclear staining was seen in the epithelioid cells (Figure 4C). No areas showing ameloblastic differentiation were noted. On the basis of these features, the incisional biopsy analysis was signed out as "malignant neoplasm, most consistent with spindle cell carcinoma," with a comment that spindle cell carcinoma was exceptionally rare in a patient of this age.

The patient underwent left hemimandibulectomy with selective neck dissection and reconstruction in May 2015. Microscopic evaluation of the surgical specimen revealed a cystic neoplasm with histologic features of plexiform ameloblastoma (Figure 4D). In one area, the neoplastic cells appeared to transition into a hypercellular sarcomatoid population (Figure 4E). Mild nuclear pleomorphism and occasional mitotic figures were noted in the sarcomatoid cells; because of decalcification of the specimen, a proliferative index was not performed. The diagnosis was revised to "spindle cell variant of ameloblastic carcinoma." The patient's tumor has not recurred at 42 months' postoperative follow-up.

Case 3

A 51-year-old woman presented to the University of Texas Southwestern Medical Center with a history of a longstanding mandibular mass. During her childhood, the patient had a benign cyst removed from this site. According to the patient, the cyst had grown slowly over several decades, and she had experienced rapid growth during the past 2 months. The patient's medical history was otherwise noncontributory. Clinical examination revealed a large, friable mass arising from the left mandible, extending to the lingual alveolar ridge and the left retromolar trigone. CT showed a large multilobulated cystic mass with solid zones arising from and replacing much of the left mandible (Figures 5A and 5B).

Incisional biopsy showed a malignant spindled neoplasm with no specific differentiation on hematoxylin and eosin staining (Figure 6A). The tumor cells showed positive immunoreactivity for AE1/AE3 and Cam 5.2 and were negative for p40, CK5/6, S100, desmin, actin, and anaplastic lymphoma kinase. As cytokeratin was expressed in the tumor cells, the incisional specimen was designated "malignant spindle cell neoplasm, favoring sarcomatoid carcinoma."

In October 2017, the patient underwent a partial mandibulectomy and selective neck dissection, followed by left fibular free flap reconstruction. Histologically, a cystic neoplasm lined by cells demonstrating the typical features of plexiform ameloblastoma in focal areas was seen (Figure 6B). Much of the tumor consisted of predominantly spindled cells growing in vague fascicles, with marked nuclear pleomorphism and hyperchromasia. There were foci of transition identified between the invasive epithelioid population and the sarcomatoid component (Figure 6C). Lymphovascular invasion was identified, but perineural invasion was not. IHC showed an epithelial component that was strongly reactive with AE1/AE3, and staining was greatly reduced in the sarcomatoid population (Figure 6D). In contrast, the sarcomatoid cells were diffusely reactive with vimentin, whereas staining was significantly decreased in the epithelial cells (Figure 6E). Additionally, the epithelial cells expressed p40, whereas the spindled cells did not. A MIB-1 proliferative index revealed variation in staining amongst different areas of the tumor. Overall, the proliferative index was estimated at 25% to 30%. A diagnosis of SCAC arising from an ameloblastoma was made. The patient received postoperative radiation therapy, but continued clinical expansion indicated recurrence of her tumor. Recently, she was diagnosed with numerous metastatic foci in her lungs, and she is being treated with combination carboplatin and paclitaxel chemotherapy.
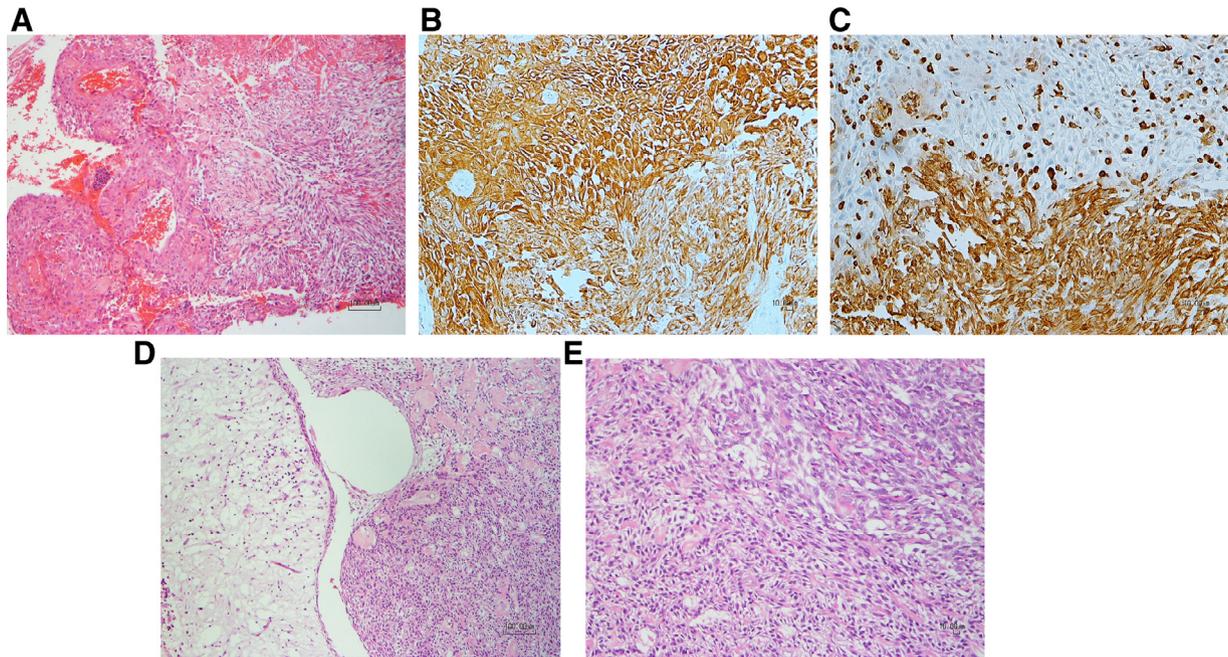
Fig. 4. Histologic features of case 2. **A,** incisional biopsy showed a hypercellular proliferation of epithelioid and sarcomatoid cells (hematoxylin and eosin [H&E], original magnification × 10). **B,** AE1/AE3 was strongly positive in the carcinomatous cells, and intensity decreased in the sarcomatoid cells (original magnification × 20). **C,** Vimentin showed strong reactivity in sarcomatoid cells, and scattered nuclear staining was seen in the epithelial cells (original magnification × 20). **D,** The excisional specimen showed a neoplasm in the pattern of plexiform ameloblastoma, with a cystic component (H&E, original magnification × 10). **E,** A morphologic transition between the epithelial and spindled populations was noted (H&E, original magnification × 20). *High resolution versions of the following slides for use with the Virtual Microscope are available as eSlides*: (A) *VM05503* (B) *VM05502* (C) *VM05500* (D) *VM05501* (E) *VM05501*.

DISCUSSION

By using the diagnostic criteria derived from our literature review, we identified 10 cases of SCAC (Table I).[2,7,11-17,19] It is notable that Slater first described the features of SCAC in 1999[9]; 3 cases diagnosed as AC before that time do fit the proposed diagnostic criteria for SCAC, so they are included in this review.[11-13] Three other cases that
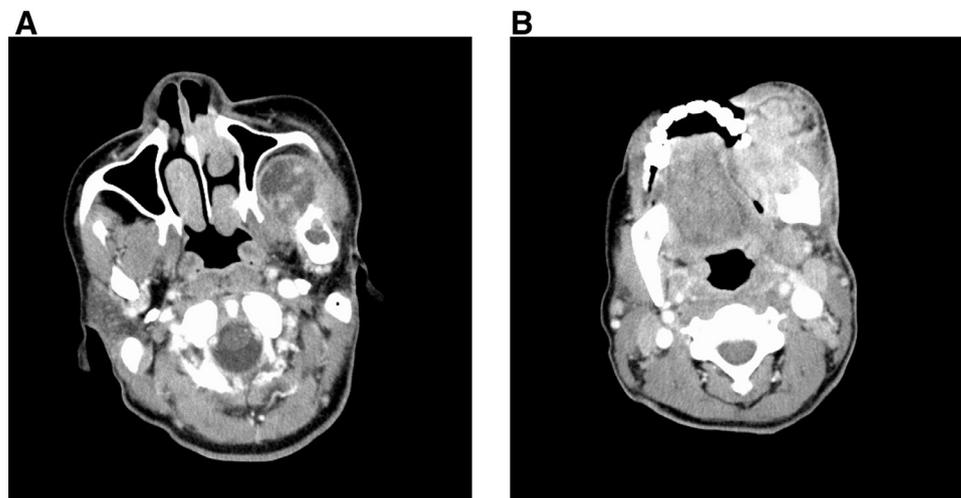

Fig. 5. Clinical presentation of case 3. **A,** The patient presented with a large multilocular lesion originating in the posterior mandible, occupying the infratemporal space on computed tomography (CT) imaging. **B,** The tumor has perforated the cortical bone of the mandible and extended into soft tissue, as seen on this paraoblique axial CT image.
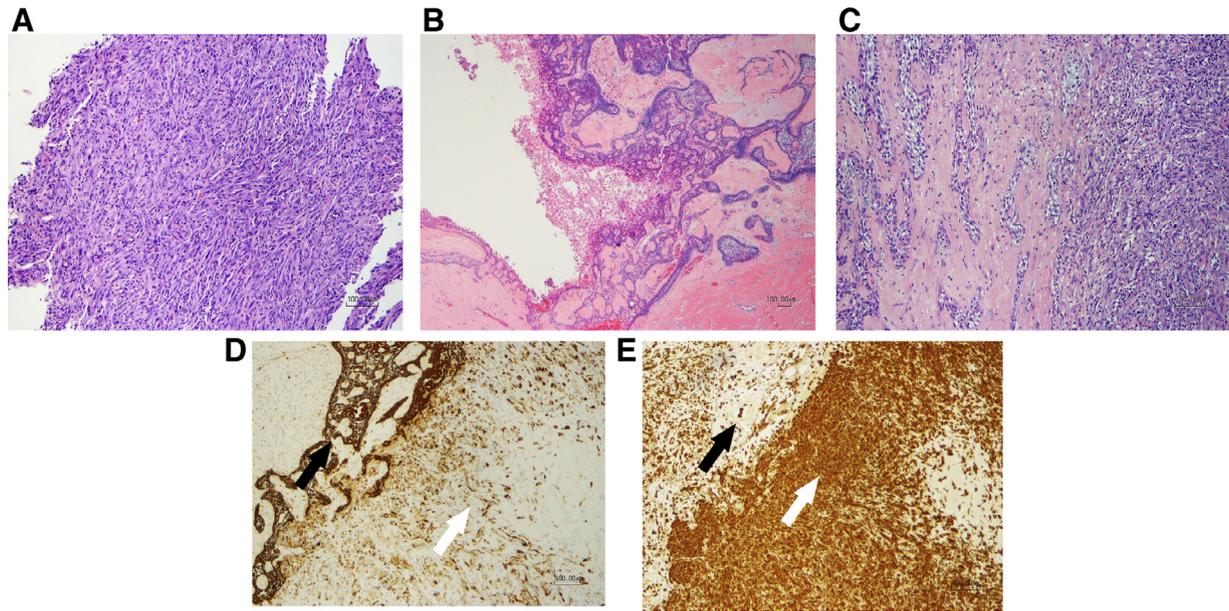
Fig. 6. Histologic features of case 3. **A,** The incisional biopsy revealed an atypical sarcomatoid proliferation with scattered chronic inflammatory cells (hematoxylin and eosin [H&E], original magnification × 10). **B,** The excisional specimen showed a cystic neoplasm with features of plexiform ameloblastoma (H&E, original magnification × 4). **C,** Foci of transition between the epithelial and sarcomatoid populations were observed (H&E, original magnification × 10). **D,** AE1/AE3 was strongly reactive in carcinoma cells (black arrow), and expression decreased in the spindled cells *(white arrow)* (original magnification × 10). **E,** Vimentin was strongly expressed in the sarcomatoid cells (white arrow), and intensity significantly decreased in the carcinoma cells (black arrow) (original magnification × 10). *High resolution versions of the following slides for use with the Virtual Microscope are available as eSlides*: (A) *VM05499* (B) and (C) *VM05498* (D) *VM05497* (E) *VM05487*.

were previously reported as SCAC do not provide convincing histologic evidence of SCAC. Slootweg and Muller reported 2 cases in 1984, the second of which has been referenced as the first reported case of SCAC.[10] In that second case, the male patient had a tumor of the right mandible, which histologically showed ameloblastomatous differentiation and cytomorphologic features of malignancy; but no spindle cell population was described.[10] This is most likely a case of conventional AC, and therefore, it is not included in this review. However, the first case in the same publication (that of a woman with a left mandibular swelling) *does* include a description of spindled cells with an ameloblastomatous proliferation.[7,10,14,15,17,19] Slootweg and Muller stated that the "compact fields of spindle-shaped cells ... showed transition into small nests of pleomorphic cells ... that assumed a columnar morphology." As this satisfies the diagnostic criteria that we adopted, this case likely represents the first report of SCAC and is included in this review. Kawauchi et al.[20] reported the case of a male patient with a mandibular tumor, described as a proliferation of spindle-shaped sarcomatoid cells, with nests of epithelial carcinomatous cells. Ameloblastic differentiation was not described, so this tumor cannot be classified as SCAC and, therefore, was not

included in this review. Last, Jindal et al.[19] reported a case of low-grade SCAC in the mandible of a female patient. These authors stated that "the spindled nuclei were cytologically bland ... . Some of the spindled cells showed hyperchromatism and nuclear pleomorphism ... ."[19] The photomicrographs showed features of ameloblastoma, but evidence of malignant cytomorphology was not demonstrated, so this case was not included in this review. The addition of the current 3 cases yields a total of 13 reported cases of SCAC.

The clinical and histopathologic features and follow-up information for all SCAC cases are listed in Table I. The mean age of patients with SCAC at diagnosis is 45.4 years, which is 4 years less than the mean age of patients with AC (49.2 years).[7] Seven of 13 patients with SCAC were males, and this is consistent with the slight male predilection of conventional AC.[8] A mandibular site predilection is seen in both SCAC and conventional AC.[8] All 13 patients with SCAC were treated with surgical resection, and 5 patients received radiation therapy after surgery. Two of the 13 patients with SCAC experienced recurrences of their tumors; and 1 patient died as a result of postoperative complications unrelated to his tumor.[14] Follow-up duration and information vary among previous reports, but it seems that

Table I. Spindle-cell ameloblastic carcinoma: case summaries[2,7,10-17]

Case No.	Authors, year	Age	Gender	Site	Treatment	Radiation?	Recurrence?	Metastasis?	Follow-up
1	Slootweg et al., 1984 (case 1)	52	Female	Mandible	Surgical resection	Yes	Unknown	No	Not reported
2	Nagai et al., 1991	50	Male	Mandible	Surgical resection	No	Yes	No	Not reported
3	Infante-Cossio et al., 1998	69	Female	Maxilla	Surgical resection	Yes	No	No	Alive 5 years post-op
4	Lau et al., 1998	23	Male	Mandible	Surgical resection	No	No	No	Alive 5 years post-op
5	Ismail et al., 2009	21	Female	Mandible	Surgical resection	No	No	Unknown	Alive 3 years post-op
6	Kamath et al., 2012	75	Male	Mandible	Surgical resection	No	No	No	Died 2 weeks post-op
7	Matsushita et al., 2015	69	Male	Mandible	Surgical resection with neck dissection	Yes	No	No	Alive 1 year 11 months post-op
8	McNaught et al., 2015	53	Male	Mandible	Surgical resection	No	No	No	Alive 4 years post-op
9	Ansari et al., 2015	60	Male	Maxilla	Surgical resection	No	Unknown	No	Not reported
10	Kiresur et al., 2017	32	Female	Mandible	Surgical resection	No	No	No	Alive 14 months post-op
11	McLean-Holden et al., 2018	23	Male	Maxilla	Surgical resection with selective neck dissection	Yes	No	No	Alive 3 years 6 months post-op
12	McLean-Holden et al., 2018	12	Female	Mandible	Surgical resection with selective neck dissection	No	No	No	Alive 3 years 6 months post-op
13	McLean-Holden et al., 2018	51	Female	Mandible	Surgical resection with selective neck dissection	Yes	Yes	Yes, to lungs	Alive 14 months post-op

post-op, postoperatively.

patients with SCAC do reasonably well after surgical treatment as long as they are closely monitored.[2,7,11-17,19]

IHC studies are performed with some frequency in the evaluation of AC and SCAC. CK19 is a cytokeratin marker typically used to demonstrate the odontogenic nature of the epithelial proliferation, but both benign ameloblastoma and AC may demonstrate reactivity.[1] More recently, the diffuse nuclear staining pattern of SOX2 has been shown to exhibit 77% sensitivity in distinguishing between AC and ameloblastoma.[21] However, SOX2 overexpression has been noted in several types of head and neck cancers, including oral squamous cell carcinoma; therefore, the ability of this marker to distinguish AC from other carcinomas is limited.[22] Calretinin positivity is noted in about half of AC cases, according to a recent study.[21] However, that study also evaluated calretinin expression in benign ameloblastoma, and 43% of cases showed positivity. Therefore, calretinin is not a good marker to distinguish between benign and malignant ameloblastomatous tumors. Calretinin also shows reactivity in several other carcinoma types, such as carcinomas of the kidney and lung.[21] Despite its lack of specificity, vimentin has been used several times in the workup of suspected cases of SCAC to evaluate the spindle-cell population found in this tumor.[13-15,20]

A second reason for using vimentin in our case series is that vimentin (an intermediate filament expressed in mesenchymal cells) is a known marker of EMT.[23] EMT is "a biologic process that allows a polarized epithelial cell ... to undergo multiple biochemical changes that enable it to assume a mesenchymal cell phenotype, and this process includes enhanced migratory capacity, invasiveness, elevated resistance to apoptosis, and greatly increased production of extracellular matrix components."[24-28] EMT is a highly regulated process that occurs during normal embryogenesis, wound healing, and tumorigenesis.[26,29] EMT upregulation has been correlated with the more aggressive biologic behavior of several cancers, resulting in worse clinical outcomes.[29-32]

The SCAC in case 1 showed a smooth cytomorphologic transition between the epithelial and sarcomatoid cell populations. Cytokeratin and vimentin studies in the current cases demonstrated the gradual changes in protein expression correlating with the cytomorphologic change from epithelial to spindled (see Figures 2C and 2D). These findings provide evidence of EMT in SCAC. The sarcomatoid populations in cases 2 and 3 showed reduced cytokeratin expression, compared with the intensity of cytokeratin expression in the epithelial populations (see Figures 4B and 6D), while coexpressing vimentin in the cytoplasm (see Figures 4C and 6E). Whether the presence of EMT in SCAC indicates a more aggressive disease course

in patients with SCAC is unknown. Further investigation of the biochemical mechanisms that govern EMT in SCAC is needed to improve our understanding of this disease process.

CONCLUSIONS

SCAC is an exceedingly rare odontogenic malignancy that has not yet been clearly defined in the literature. Here, we reported 3 additional cases of SCAC, bringing the total number of verified SCAC cases to 13. On the basis of a literature review and our findings, we propose 2 criteria to aid in the diagnosis of SCAC: (1) a carcinoma with ameloblastic differentiation must be observed; and (2) that carcinoma must be intimately associated with or give rise to a spindle-cell population that is part of the neoplastic proliferation (distinct from the background stroma). Histologic evidence of EMT is also found in SCAC, as demonstrated by the changes in protein expression of the epithelioid and sarcomatoid tumor cells. It is essential to increase our understanding of the biologic behavior of SCAC so that we can provide optimal treatment and achieve the best clinical outcomes for patients with this diagnosis.

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