Original Article

Fine Needle Aspiration of Salivary Gland Carcinomas With High-Grade Transformation: A Multi-institutional Study of 22 Cases and Review of the Literature

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BACKGROUND: High-grade transformation (HGT) is a rare process whereby conventional low- to intermediate-grade salivary gland carcinomas (SGC) transform into high-grade, poorly or undifferentiated malignancies with focal or complete loss of their conventional histomorphologic features. Because tumors with HGT are associated with a worse prognosis than their conventional counterparts, preoperative recognition of HGT may be of benefit for optimal patient management. Using a multi-institutional approach, we describe the largest fine needle aspiration (FNA) cohort of salivary gland carcinomas with HGT. **METHODS:** The archives of 9 large academic medical centers were searched, and 22 cases of SGC with HGT were identified by surgical excision accompanied by preoperative FNA. Clinical and cytomorphologic features were retrospectively reviewed. **RESULTS:** The male-to-female ratio was 14:8, and the mean patient age was 60.2 years. The average tumor size was 3.6 cm, and 19 cases were from the parotid gland. Acinic cell carcinoma with HGT was the most common tumor subtype, comprising 12 cases with HGT, followed by adenoid cystic carcinoma, secretory carcinoma, and other subtypes. Eighteen cases were classified as malignant; however, a specific diagnosis of HGT was not made. Sixteen cases contained a high-grade cytologic component, and 7 cases had a mixture of both conventional and high-grade components retrospectively. **CONCLUSIONS:** SGC with HGT should be considered in the differential diagnosis of a salivary gland aspirate exhibiting high-grade cytomorphologic features. The presence of distinct tumor populations, conventional and high-grade, should prompt consideration of HGT, especially when the conventional component is acinic cell carcinoma or adenoid cystic carcinoma. *Cancer Cytopathol* 2021;129:318-325. © 2020 American Cancer Society.

KEY WORDS: acinic cell carcinoma; adenoid cystic carcinoma; fine needle aspiration; high-grade transformation; salivary cytology; salivary gland; salivary gland carcinoma; secretory carcinoma.

INTRODUCTION

Primary salivary gland carcinoma (SGC) is classified in the most recent *WHO Classification of Head and Neck Tumours* into 21 tumor types.[1,2] While salivary duct carcinoma is an inherently high-grade, aggressive carcinoma,[3] most subtypes of SGC are known to be biologically low- to intermediate-grade. However, these lower-grade SGCs can occasionally transform into high-grade malignancies associated with marked cellular

atypia, hyperchromasia, and increased mitotic activity. This phenomenon is termed high-grade transformation (HGT), and greater than 100 cases, mostly as case reports and small series, involving acinic cell carcinoma (AcCC), adenoid cystic carcinoma (AdCC), and several other tumor types have been reported in the literature.[4-7] The transformed component presents histologically as a poorly differentiated or undifferentiated carcinoma with at least partial loss of the original characteristic histomorphologic phenotype.[4,5,7]

From a clinical perspective, HGT is known to impart more aggressive biologic behavior and a worse prognosis than conventional low- to intermediate-grade SGC.[4,6-8] Preoperative recognition of a high-grade component by fine needle aspiration (FNA) would therefore be useful for patient prognostication as well as for influencing patient management, including presurgical planning.[9] Despite wide recognition of this disease concept, only a few case reports describing the cytological features of SGC with HGT have been published,[10-17] and comprehensive FNA case series are lacking. Using a multi-institutional approach, we describe the clinical and cytomorphologic features of the largest FNA series of SGC with HGT and provide a comprehensive review of the literature.

MATERIAL AND METHODS

The institutional review boards of each collaborating institution approved the current study. We performed a retrospective search of the institutional pathology archives of nine large academic medical centers (Massachusetts General Hospital [Boston, Massachusetts], Stanford University Medical Center [Palo Alto, California], Hospital of the University of Pennsylvania [Philadelphia, Pennsylvania], University of Wisconsin School of Medicine and Public Health [Madison, Wisconsin], Beth Israel Deaconess Medical Center [Boston, Massachusetts], Dartmouth-Hitchcock Medical Center [Lebanon, New Hampshire], Vanderbilt University Medical Center [Nashville, Tennessee], Agostino Gemelli School of Medicine [Rome, Italy], and University of Michigan-Michigan Medicine [Ann Arbor, Michigan]) from 1997 to 2020 for SGC with HGT and corresponding FNA material. The surgical pathology slides of the tumors were reviewed by 3 head and neck pathologists (MN, WCF, and PMS), and

cases fulfilling the histomorphologic criteria for SGC with HGT as defined in the previous studies and by the World Health Organization[4,6,7,18-22] were included in the study cohort. Twenty-two tumors from 22 patients with HGT on excision with preoperative FNA met the inclusion criteria. Sixteen of the cohort cases were from primary salivary gland tumors, and 6 FNA cases were from recurrent lesions with a documented primary tumor, all from distinct patients. The diagnosis of HGT was established either in the primary tumor excision specimen or in tissue from tumor recurrence or metastasis. The FNA diagnostic classifications were based on data from the original cytopathology reports adjusted to the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC).[2] Twenty of the FNA cohort cases with slides available for review were examined by study authors and evaluated for a series of cytomorphologic features, including cellular cytomorphology, FNA cellularity, nuclear pleomorphism, nucleoli, nuclear/cytoplasmic ratio, and necrotic background. For the remaining 2 cases, information for diagnostic category and cytological diagnoses were collected from cytology reports.

RESULTS

Clinical and Pathologic Findings

In total, 22 tumors from 22 patients with HGT noted on excision with preoperative FNA were enrolled in this study. Clinical characteristics for the cohort of FNA cases are summarized in Table 1. The patients' age ranged from 24 to 82 years (mean, 60.2 years), with a male:female ratio of 14:8. Tumors ranged in size from 1.8 to 6.2 cm (mean, 3.6 cm). Six FNA samples were obtained from recurrent or metastatic sites, including cervical or mediastinal lymph nodes, lung, and stylomastoid foramen. Nineteen (86%) cases originated in the parotid gland, while the submandibular gland, hard palate, and maxillary sinus were the remaining 3 primary case sites (14%). The most common original conventional tumor type was AcCC (n = 12 [55%]), followed by AdCC (n = 5 [23%]), secretory carcinoma (n = 2 [9%]), and epithelial-myoepithelial carcinoma, mucoepidermoid carcinoma, and clear cell carcinoma (n = 1 [4.5% each]). A high-grade component comprised >50% of tumor areas in the corresponding surgical resection specimen in 50% of cases (n = 11 [7

TABLE 1. Clinical and Pathologic Characteristics of Salivary Gland Carcinoma with High-Grade Transformation

Characteristic	Values
Gender, n (%)	
Male	14 (64)
Female	8 (36)
Age, y, mean (range)	60.2 (24-82)
Tumor size, cm, mean (range)	3.6 (1.8-6.2)
Original tumor site, n (%)	
Parotid gland	19 (86)
Submandibular gland	1 (4.5)
Hard palate	1 (4.5)
Maxillary sinus	1 (4.5)
Histology, n (%)	
AcCC-HGT	12 (55)
AdCC-HGT	5 (23)
SC-HGT	2 (9.0)
EMC-HGT	1 (4.5)
MEC-HGT	1 (4.5)
CCC-HGT	1 (4.5)
High-grade component, n (%)	
0%-10%	4[a] (18)
>10%-50%	7[b] (32)
>50%-100%	11[c] (50)
Postoperative therapy, n (%)	
Chemotherapy	1 (4.5)
Radiation therapy	8 (36)
Chemotherapy + radiation therapy	13 (59)
Follow-up, median (range) months	8.8 (0.8-126)
Recurrence or metastasis, n (%)	
Yes	14 (64)
No	8 (36)
Patient outcome, n (%); median follow-up, months	
Alive without disease	6 (27); 3.8
Alive with disease	7 (32); 19.7
Dead with disease	9 (41); 10.7

Abbreviations: AcCC, acinic cell carcinoma; AdCC, adenoid cystic carcinoma; CCC, clear cell carcinoma; EMC, epithelial-myoepithelial carcinoma; HGT, high-grade transformation; MEC, mucoepidermoid carcinoma; SC, secretory carcinoma.
[a]All primary.
[b]5 primary, 2 recurrent.
[c]7 primary, 4 recurrent.

TABLE 2. Cytologic Characteristics of Salivary Gland Carcinoma With High-Grade Transformation

Characteristic	Values
Diagnostic category of FNA from primary site (n = 16)	
Malignant	12 (75)
Suspicious for malignancy	1 (6.3)
Neoplasm: SUMP	3 (19)
Diagnostic category of FNA from recurrent site (n = 6)	
Malignant	6 (100)
Tumor grading (n = 22)	
High	7 (32)
Intermediate to high	1 (4.5)
Intermediate	2 (9)
Low to intermediate	1 (4.5)
Low	1 (4.5)
Not graded	10 (45)
Preoperative diagnosis of HGT (n = 22)	
Yes	0 (0)
No	22 (100)
Specific diagnosis of tumor subtype (n = 22)	
Yes	3 (14)
No	19 (86)
FNA cellularity (n = 20)	
Low	3 (15)
Moderate	2 (10)
High	15 (75)
Groups or single cells (n = 20)	
Groups	7 (35)
Single cells	0 (0)
Both	13 (65)
Cellular component (n = 20)	
LG + HG	7[a] (35)
HG only	9[b] (45)
LG only	4[c] (20)
Nuclear pleomorphism (n = 20)	
Present	12 (60)
Absent	8 (40)
Nucleoli (n = 20)	
Prominent	11 (55)
Small or inconspicuous	9 (45)
High nuclear/cytoplasmic ratio (n = 20)	
Present	18 (90)
Absent	2 (10)
Necrotic background (n = 20)	
Present	8 (40)
Single cell necrosis/ inflammatory	3 (15)
Absent	9 (45)

Abbreviations: FNA, fine needle aspiration; HG, high-grade component; HGT, high-grade transformation; LG, low-grade component; SUMP, salivary gland neoplasm of uncertain malignant potential.
All values are presented as n (%).
[a]5 primary, 2 recurrent.
[b]5 primary, 4 recurrent.
[c]All primary.

primary, 4 recurrent]), >10% to 50% of the tumor in 32% (n = 7 [5 primary, 2 recurrent]), and 0% to 10% of the tumor in 18% (n = 4 [all primary]) of the cohort cases. Among cases with available clinical treatment and follow-up data, all patients received postoperative chemotherapy and/or radiotherapy, and 14 (64%) patients experienced cancer recurrence or metastasis. Six (27%) of the patients were alive without disease, 7 (32%) were alive with disease, and 9 (41%) died of the disease with follow-up periods of 0.8 to 126 months (median, 8.8 months).

Cytomorphologic Findings

Cytomorphologic findings of the FNA cohort cases are summarized in Table 2, and corresponding representative cytologic features are shown in Figures 1 and 2. The FNA from the primary tumor (n = 16) was classified as malignant in 12 (75%) cases, followed by salivary gland neoplasm of uncertain malignant potential (SUMP) in 3 (19%) cases, and suspicious for malignancy in 1 (6.3%) case by the MSRSGC.[2] By original report, among 22 FNAs, 7 (32%) were designated as high-grade, but a specific diagnosis of HGT was not suggested. The definitive cytologic diagnosis of
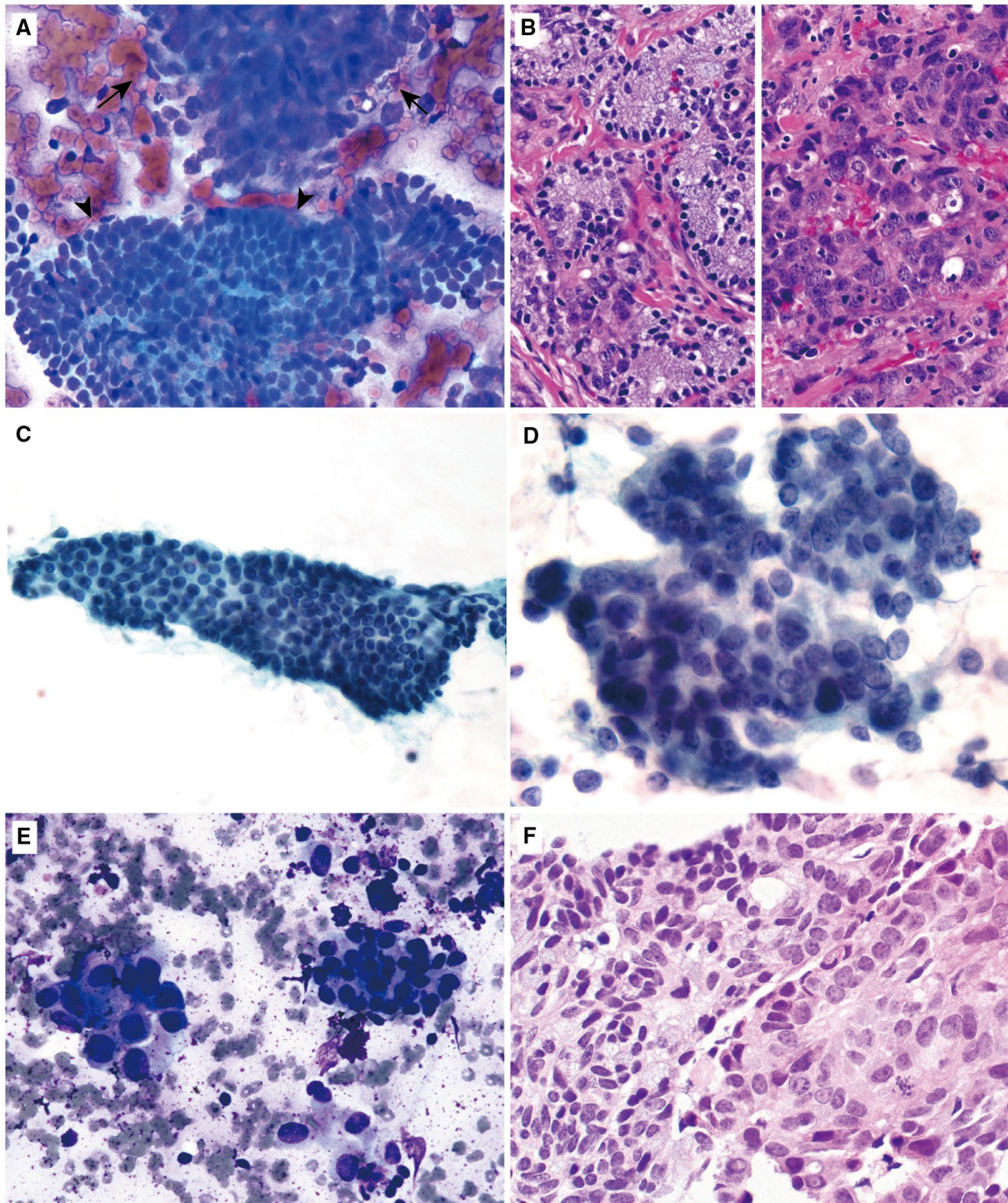
Figure 1. Cytologic features of high-grade transformation (HGT) exhibiting 2-cell patterns. (A) FNA of acinic cell carcinoma with HGT. Tumor cells from a high-grade component (arrow) have larger nuclei and form disorganized cellular clusters compared with the conventional component (arrowhead) (Papanicolaou stain). (B) Histologic features of the same case (hematoxylin and eosin stain). The tumor loses features of acinic cell carcinoma (left panel) and transforms into poorly differentiated carcinoma (right panel). (C, D) Higher magnification of conventional and high-grade components of acinic cell carcinoma with HGT (Papanicolaou stain). Tightly cohesive clusters of uniform basaloid cells with small nuclei suggestive of low-grade carcinoma (C). Large pleomorphic cells with occasional prominent nucleoli form less cohesive clusters or are present as single cells (D). (E) Diff-Quik stain of secretory carcinoma with HGT. Two cell populations with different sizes and chromatin patterns are observed. (F) Cell block specimen of an FNA of acinic cell carcinoma with HGT. A clear contrast between 2 components is demonstrated. Mitosis is noted in the high-grade component (hematoxylin and eosin stain).
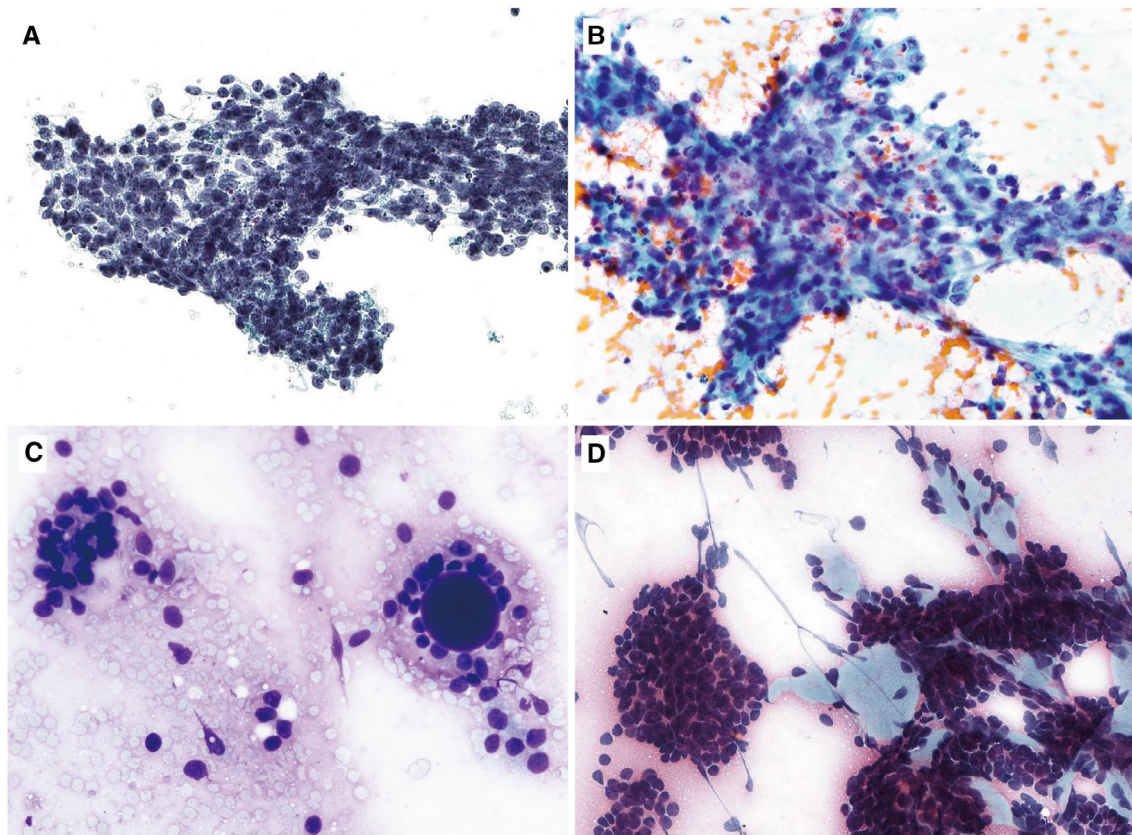
Figure 2. Cytologic features of high-grade transformation (HGT) with 1 component. (A, B) FNA of HGT showing solely the high-grade carcinoma component (Papanicolaou stain). (A) FNA of adenoid cystic carcinoma with HGT. Large pleomorphic are present in clusters with nuclear crowding. Inflammatory cells and necrotic debris are noted. (B) FNA of acinic cell carcinoma with HGT. The original acinic cell differentiation is completely lost and the cytologic features are indistinguishable from those in panel A. (C, D) FNA of adenoid cystic carcinoma with HGT showing only the conventional carcinoma component. (C) Basaloid hyperchromatic cells are present around matrix globules. This case was signed out as adenoid cystic carcinoma (Diff-Quik stain). (D) Cohesive clusters occasionally associated with matrix-like material. Although slight nuclear size variation is noted, no obvious high-grade features are observed (Papanicolaou stain).

a conventional tumor subtype was rendered in 3 cases regardless of the tumor grading: 1 recurrent secretory carcinoma, 1 AcCC diagnosed by immunohistochemistry using the cell block material, and 1 AdCC with characteristic cytomorphologic features of AdCC. The diagnoses of the other FNAs were descriptive without specifying tumor subtypes.

In the retrospective slide evaluation, 85% of the FNA cohort was moderately or highly cellular (n = 17). All aspirates (n = 20) contained cohesive groups of neoplastic cells with or without a component of isolated cells. Thirty-five percent (n = 7 [5 primary, 2 recurrent]) of HGT cases contained cells representing both the conventional low-grade tumor and high-grade component (Fig. 1). In contrast, 45% of HGT FNAs (n = 9 [5 primary, 4 recurrent]) were composed of only cells from the high-grade component (Fig. 2A,B), and 20% (n = 4 [all primary]) of cases contained neoplastic cells only from the conventional low-grade component (Fig. 2C,D). In total, 16 (80%) cases contained cells from the high-grade component. Tumor cells representing HGT were disorganized and less cohesive and had larger and more pleomorphic nuclei with conspicuous nucleoli and occasional mitoses compared with the conventional low-grade SGC component. Among the HGT components, nuclear pleomorphism, prominent nucleoli, high nuclear/cytoplasmic ratio, and necrotic background were present in 12 (60%), 11 (55%), 18 (90%), and 8 (40%) FNA cases, respectively. Among all 22 FNA cases, cell blocks were prepared in 16 (73%) cases, and ancillary studies were performed in 7 (32%) cases, including immunohistochemical stains (n = 7) and fluorescence in situ hybridization (n = 3).

TABLE 3. Cytologic features of Salivary Gland Carcinoma with High-Grade Transformation in Previous Studies

	Histology	Diagnostic Category	Cytologic Diagnosis	Cell Component	Nuclear Pleomorphism	Prominent Nucleoli	High Nuclear/ Cytoplasmic Ratio	Background
González-Peramato et al[10]	AcCC-HGT	Malignant	Salivary carcinoma, AcCC, and high-grade carcinoma	LG + HG	Present	Present	Present	Lymphoid
Malhotra et al[11]	AdCC-HGT	Malignant	Adenocarcinoma NOS, undifferentiated carcinoma	LG + HG	Present	Present	Present	Hemorrhagic
Johnykutty et al[12]	AcCC-HGT	Malignant	High-grade salivary gland neoplasm	LG + HG	Present	Present	Present	NS
Suzuki et al[13]	EMC-HGT	Malignant	NS	LG + HG	Present	Present	NS	NS
Jung et al[14]	SC-HGT	Malignant	NS	HG only	Present	Present	Present	Clear
Bhardwaj et al[15]	AdCC-HGT	Malignant	Poorly differentiated carcinoma	LG + HG	Present	Present	NS	Necrotic, myxoid matrix
Dutta et al[16]	AdCC-HGT	Malignant	Basaloid neoplasm, AdCC/basal cell adenocarcinoma	Presumably LG only	Absent	Absent	Present	NS
Pusztaszeri et al[17]	AdCC-HGT	Malignant	AdCC-HGT	LG + HG	Present	Present	NS	Histiocytic, lymphoid

Abbreviations: AcCC, acinic cell carcinoma; AdCC, adenoid cystic carcinoma; EMC, epithelial-myoepithelial carcinoma; HG, high-grade component; HGT, high-grade transformation; LG, low-grade component; NOS, not otherwise specified; NS, not stated; SC, secretory carcinoma.

DISCUSSION

FNA is considered an effective and informative method for the preoperative evaluation of salivary gland tumors. It is useful not only in helping to differentiate malignant tumors from benign tumors, but also for distinguishing high-grade carcinomas from those that are low-grade, guiding treatment management.[23] HGT is histologically characterized by the transformation of a conventional carcinoma (low- to intermediate-grade) into a high-grade, poorly differentiated or undifferentiated carcinoma.[4,5] Published reports indicate that the most common SGC subtypes in cases of HGT are AcCC and AdCC.[5-7] In our FNA cohort, AcCC was the predominant HGT-associated tumor subtype followed by AdCC. In this sense, aspirates of cases identified as AcCC or AdCC with unusual higher-grade features should prompt consideration that the case might represent HGT and warrant comment in the cytologic report.

The cytomorphologic findings of HGT from previous reports are summarized in Table 3.[10-17] Among 8 single case reports, all FNA specimens, except for 1 report of metastatic SGC with HGT in pleural effusion cytology,[17] were from primary salivary gland tumors.[10-16] All reported FNA specimens were diagnosed as malignant. A retrospective analysis of the reported cases revealed 2 morphological components—a lower-grade conventional carcinoma and a component with HGT—in 6 cases, solely cells from the HGT component in 1 case, and solely cells from the conventional component in 1 case. Cytological diagnoses of high-grade or poorly differentiated carcinomas were made in 6 cases, and HGT was suggested in 2 cases, including 1 recurrent case.

Although HGT itself is associated with a poor clinical prognosis,[4,6,7,21] there are no data regarding the percentage of high-grade component that influences patient prognosis. In our cohort, the proportion of HGT component determined on the excision specimen varied from those with a limited HGT component to those that were almost exclusively composed of an HGT component (Table 1). Although our cohort of primary tumors is limited (n = 16) in terms of overall cohort size and length of follow-up, and although the true clinical significance should bear out in follow-up studies with an expanded cohort, the relationship between clinical outcomes and the proportion of high-grade component in the primary tumor resection specimen is presented and summarized in

TABLE 4. Clinical Outcomes and Proportion of High-Grade Component in Primary Tumor (n = 16)

High-Grade Component	Recurrence or Metastasis, n		Patient Outcome, n		
	Yes	No	Alive Without Disease	Alive With Disease	Dead With Disease
0%-10%	1	3	3	0	1
>10%-50%	2	3	2	1	2
>50%-100%	5	2	1	3	3

The median follow-up was 6.8 months. The proportion of high-grade component was calculated on the resection specimen.

Table 4. Patients with primary tumors with a lower proportion of high-grade component tended to have lower recurrence/metastasis rate and lower overall mortality, with a median follow-up of just 6.8 months. We present these data as part of the discussion as an intriguing consideration to include the percentage of HGT on surgical resections as a possible prognostic indicator.

Certainly, the extent of HGT component in the FNA specimen would be expected to influence the diagnostic accuracy of the FNA, at least in terms of grading the lesion. Thirty-five percent of cases in our cohort (n = 7) and 6 of 8 previously reported FNA cases contained both tumor components (conventional tumor and HGT [Table 3]). On the other hand, 20% of cases in our cohort (n = 4) and 1 of 8 previously reported cases contained only the conventional low- to intermediate-grade component of SGC, which represents a sampling-related pitfall for identifying the carcinoma as high-grade preoperatively. The proportion of HGT component in these 4 excision cases in our study was ≤10% in 2 cases and >10% to 50% in 2 cases. While specific interpretation of HGT may seem elusive, this entity should be included in the differential diagnosis of a high-grade SGC, especially for those cases comprising 2 distinct epithelial components: a conventional low- to intermediate-grade type admixed with a high-grade subpopulation.

The differential diagnosis of HGT includes salivary duct carcinoma, high-grade mucoepidermoid carcinoma, a subset of myoepithelial carcinomas, adenocarcinoma not otherwise specified, and metastatic cancers from other anatomic sites. From a clinical perspective, it is more important for management purposes that the FNA identifies the neoplasm as high-grade than it is to give a specific diagnosis of HGT.[24,25] In our cohort with available FNA slides, a high-grade component was detected in 80% of cases (16/20 cases). Although the distinction is usually of less clinical importance except perhaps for metastatic carcinomas, the distinction of HGT cases from salivary duct carcinoma may influence pre- and postoperative management, including the use of androgen receptor– and HER2-targeted therapy.[3] Abundant eosinophilic cytoplasm and immunoexpression of androgen receptor, GATA3, GCDFP-15, and HER2 using cell block material can assist in distinguishing salivary duct carcinoma from SGC with HGT.[3] The specific diagnosis of a conventional tumor component, especially AcCC or AdCC, was given in 3 of our cohort cases using ancillary studies performed on cell block material. Although the diagnosis of a conventional tumor subtype may not be necessary, ancillary immunohistochemistry or fluorescence in situ hybridization can help to establish the diagnosis of a primary SGC and exclude the possibility of metastasis.[26,27]

Given that many conventional SGCs are characterized by specific genetic alterations, ancillary studies on cell block materials are useful to establish the diagnosis.[26,28] Based on the discovery of an *NR4A3* translocation in AcCC,[29] a recent study demonstrated the usefulness of *NR4A3* FISH and NR4A3 IHC in FNA specimens.[27] *MYB*, *NTRK3*, *MAML2*, and *EWSR1* FISH might have facilitated a diagnosis of AdCC, secretory carcinoma, mucoepidermoid carcinoma, or clear cell carcinoma in our FNA cohort.[26] The definitive diagnosis of conventional carcinoma with a high-grade component would suggest the possibility of HGT. Although we did not investigate the molecular features of our FNA cohort, future studies exploring the molecular biology of SGC with HGT may prove fruitful, and perhaps, such studies would reveal a molecular signature for HGT that could be applied to FNA cases.

In conclusion, SGC with HGT should be considered in the differential diagnosis of salivary gland aspirates of high-grade carcinomas, especially when the high-grade component has an undifferentiated appearance. The presence of 2 distinct morphological tumor components (a conventional component and a high-grade component) should prompt consideration for HGT—especially when the conventional component is AcCC or AdCC—and, importantly, it should also prompt consideration of a diagnostic comment about this possibility in the cytology report.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHORS' CONTRIBUTIONS

Masato Nakaguro: Background research, study conception and design, collation of cases, writing–original draft, writing–review and editing. **William C. Faquin:** study conception and design, collation of cases, writing–review and editing. **Zubair W. Baloch:** Collation of cases, writing–review and editing. **Richard L. Cantley:** Collation of cases, writing–review and editing. **Margaret L. Compton:** Collation of cases, writing–review and editing. **Kim A. Ely:** Collation of cases, writing–review and editing. **Brittany J. Holmes:** Collation of cases, writing–review and editing. **Rong Hu:** Collation of cases, writing–review and editing. **Darcy A. Kerr:** Collation of cases, writing–review and editing. **Kathleen T. Montone:** Collation of cases, writing–review and editing. **Michiya Nishino:** Collation of cases, writing–review and editing. **Liron Pantanowitz:** Collation of cases, writing–review and editing. **Esther Diana Rossi:** Collation of cases, writing–review and editing. **Peter M. Sadow:** study conception and design, collation of cases, writing–review and editing.

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