Cytological features of oncocytic pleomorphic adenoma of the salivary gland: Using the Milan classification system to report 3 patients

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Abstract. Pleomorphic adenoma (PA) is the most common salivary gland tumour. Pre-operative fine-needle aspiration (FNA) is currently one of the most widely used cytological examination techniques for the diagnosis of salivary gland tumours. Because PA exhibits characteristic cytological features, cytological diagnosis is straightforward in most cases. However, limitations have emerged in certain cases, specifically in cases of oncocytic metaplasia (rare in PA), characterised by rich eosinophilic granular cytoplasm and relatively large nuclei, which can make cytological diagnosis challenging. To date, only two cytological reports of oncocytic PA have been published. The present study retrospectively analysed patients with oncocytic PA of the salivary gland who underwent preoperative FNA to describe the clinicopathological features of oncocytic PA. In addition, the application of the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) was discussed. The study cohort included 3 patients with parotid gland tumours. The cytological specimens had small and/or large clusters of oncocytic cells containing rich granular cytoplasm, relatively large nuclei, and occasional nucleoli in a myxoid (2 patients) and clear (1 patient) background, with no necrotic material. A review of the cytological features of the presented cases, as well as previously reported cases, indicated that oncocytic PA may be overdiagnosed as carcinoma, especially carcinoma ex pleomorphic adenoma (CXPA) because these cells have relatively large nuclei. The cytological features of oncocytic cells in PA resemble those of salivary duct carcinoma, the most common carcinoma component of CXPA. The absence of necrotic material and high-grade nuclear atypia are important diagnostic features. Furthermore, cytological specimens with atypical oncocytic cells in the PA should be classified as salivary neoplasms in the uncertain malignant potential category of the MSRSGC.

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Abbreviations: AUS, atypia of undetermined significance; CXPA, carcinoma ex pleomorphic adenoma; FNA, fine-needle aspiration; MSRSGC, Milan System for Reporting Salivary Gland Cytopathology; PA, pleomorphic adenoma; PLAG1, pleomorphic adenoma gene 1; ROM, risk of malignancy; SUMP, salivary gland neoplasm of uncertain malignant potential

Key words: oncocytic pleomorphic adenoma, salivary gland, fine-needle aspiration cytology, Milan classification

Introduction

Pleomorphic adenoma (PA) is the most common salivary gland neoplasm (1). Fine-needle aspiration (FNA) cytology is a well-established pre-operative approach for salivary gland tumour evaluation (2-4). The characteristic cytological features of PA, such as the presence of a biphasic cell population composed of myoepithelial and ductal cells and chondromyxoid material, are well recognised (5). Therefore, the cytological diagnosis of PA is not difficult in most cases. However, the cytological and histological features overlap with those of malignant neoplasms (including predominant cellular components without the characteristic chondromyxoid stroma and the presence of nuclear atypia); thus, diagnosis is challenging in some cases (5,6).

Oncocytes are histopathologically characterised by the presence of a rich eosinophilic granular cytoplasm owing to the abundance of mitochondria, well-defined cell boundaries, and hyperchromatic nuclei that accompany the nucleoli (7,8). In individuals aged >50 years, oncocytic metaplasia is a common finding in non-neoplastic ductal and acinar epithelial cells of the salivary gland (7,8). Moreover, Warthin's tumour, the second most common salivary gland tumour, as well as oncocytoma and oncocytic carcinomas of the salivary gland, display characteristic oncocytic morphology (9). PA occasionally presents with various types of metaplastic changes, including squamous metaplasia (5). Oncocytic metaplasia is rare in PA but can pose diagnostic challenges (7,10-14). Moreover, only two cytological

reports on oncocytic PA have been published in the English literature (15,16), and oncocytic neoplastic cells contain enlarged nuclei, leading to overdiagnosis (16).

In 2018, the Milan System for Reporting Salivary Gland Cytopathology (MSRSGC) was created as a standardised and reproducible reporting system for salivary FNA cytology specimen classification (17), with the second edition published in 2023 (18). MSRSGC risk stratification is based on the assumed risk of malignancy (ROM) and recommendations of therapeutic management for each tumour category (18). MSRSGC classifies tumours into seven diagnostic cytomorphological-specific categories: I, non-diagnostic; II, non-neoplastic; III, atypia of undetermined significance (AUS); IVA, benign neoplasm; IVB, salivary gland neoplasm of uncertain malignant potential (SUMP); V, suspicious for malignancy; and VI, malignant (18). The MSRSGC system is useful for the cytological diagnosis of salivary gland neoplasms (19-22). Oncocytic neoplastic lesions with non-specific atypical cytomorphological features are classified as SUMP (IVB) (18).

In this study, we have retrospectively analysed patients with oncocytic PA of the salivary gland that underwent preoperative FNA to describe the clinicopathological features of salivary gland oncocytic PA.

Materials and methods

Patient selection. Patients diagnosed with oncocytic PA of the salivary gland by postoperative pathological examination at Osaka Medical and Pharmaceutical University Hospital (Osaka, Japan), who underwent preoperative FNA from December 2020 to June 2023 were included in the study.

This retrospective, single-institution study was conducted in accordance with the tenets of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of Osaka Medical and Pharmaceutical University Hospital (approval #2023-073). All data were anonymised. Owing to the retrospective study design, the Institutional Review Board waived the requirement for informed consent, as medical records and archived samples were used with no risk to the participants. Moreover, the present study did not include children. Information regarding this study, such as the inclusion criteria and opportunity to opt-out, was provided using the institutional website (https://www.ompu.ac.jp/u-deps/path/img/file19.pdf).

No statistical analysis was performed in this article.

Cytological analysis. The FNA specimens were stained with Papanicolaou and Giemsa stains. The cytological characteristics of the salivary gland FNA specimens, such as background features (presence of chondromyxoid material) and types of epithelial cells, were evaluated.

MSRSGC (second edition) was used to classify FNA specimens into the following seven categories: I, non-diagnostic; II, non-neoplastic; III, AUS; IVA, benign neoplasm; IVB, SUMP; V, suspicious for malignancy; and VI, malignant (18). At least two researchers independently evaluated the cytological features of all specimens.

Histopathological analysis. Surgically resected salivary gland specimens were fixed in 10% buffered formalin, dehydrated, embedded in paraffin, sectioned, and stained with haematoxylin and eosin. At least two researchers independently evaluated the histopathological features of all specimens. Histopathological features, such as the type of epithelium and the presence of chondromyxoid material, were evaluated and compared with the cytological features of the FNA specimens. Oncocytic metaplasia was defined as the presence of neoplastic cells containing rich eosinophilic granular cytoplasm, well-defined cell boundaries, and hyperchromatic nuclei, with or without nucleoli (7,8).

Immunohistochemical analysis. Immunohistochemical analysis was performed using an autostainer (Discovery Ultra System; Roche Diagnostics) according to the manufacture's instructions. 4-micrometer sections were incubated with mouse monoclonal antibody against pleomorphic adenoma gene 1 (PLAG1) (cat. no. 3B7; Abnova, dilution; 1:50) for 20 min at room temperature. Secondary antibodies were pre-diluted and were used to incubate the sections for 8minutes at room temperature [Optivew DAB Universal Kit (cat. no. 518-11427; Roche Diagnostics)].

Results

Patient characteristics. Of the patients with PA of the salivary gland who underwent pre-operative cytological and postoperative pathological examinations at Osaka Medical and Pharmaceutical University Hospital (n=142) between December 2020 and June 2023, only 2.1% (n=3) of all patients had oncocytic PA. The clinicopathological features of the study cohort are summarised in Table I. Ultimately, the study cohort included three patients with oncocytic PA of the salivary gland (Patients 1-3). This cohort included two males and one female. The median age of the patients was 34 years (range: 22-51 years). The study population comprised two males and one female. Patients 1-3 each had a lesion in the parotid gland (one and two patients on the right and left sides, respectively). No molecular tests examining *PLAG1* fusions were performed in all three tumours.

Cytological features. The cytological features of the study samples are presented in Figs. 1-3 (Table I). Giemsa staining revealed myxoid material in two of the three patient samples. In the remaining patient, a clear background without myxoid material was observed. Necrotic material was not observed in any of the specimens. Small and/or large clusters of oncocytic cells, cytologically characterised by the presence of rich granular cytoplasm and relatively large round nuclei accompanying nucleoli, with a low nuclear/cytoplasmic ratio, were observed in all three patients (95-100% of the epithelial cells present in the cytological specimens were oncocytic cells). Metachromatic material, revealed by Giemsa staining, was also present around these oncocytic cells. A small number of conventional bland myoepithelial and ductal cells were observed in two of the three patient samples. No mitotic figures were observed in any specimen.

The initial cytological diagnosis according to MSRSGC (18) was SUMP (category IVB) in patient 1 and suspicious for malignancy (category V) (especially carcinoma ex pleomorphic adenoma (CXPA)) in patients 2 and 3.

Table I. Clinicocytological and pathological features of oncocytic pleomorphic adenoma of the salivary gland in the present series and previously reported patients.

				Cytological features						Histopathological features		
First author/s, year	Patient	Age, years	Sex	Background	Epithelial cells	Oncocytic cells	Conventional myoepithelial cells	Conventional ductal cells	Initial MSRSGC	Oncocytic cells, %	Chondromyxoid material	(Refs.)
Present study	1	22	Male	Clean	Small clusters	95%	2%	3%	IVB	30	+	-
Present study	2	34	Male	Myxoid material	Small and large clusters	100%	None	None	V	60	+	-
Present study	3	51	Female	Myxoid material	Small clusters	95%	5%	None	V	60	+	-
Jiménez-Heffernan*et al*, 2001	4	61	Male	Myxoid material	NA	100%	None	None	NA	>85	+	(15)
Ito *et al*, 2020	5	62	Female	Myxoid material	NA	Present	Present	None	VI	80	+	(16)

MSRSGC, Milan System for Reporting Salivary Gland Cytopathology; NA, not available.

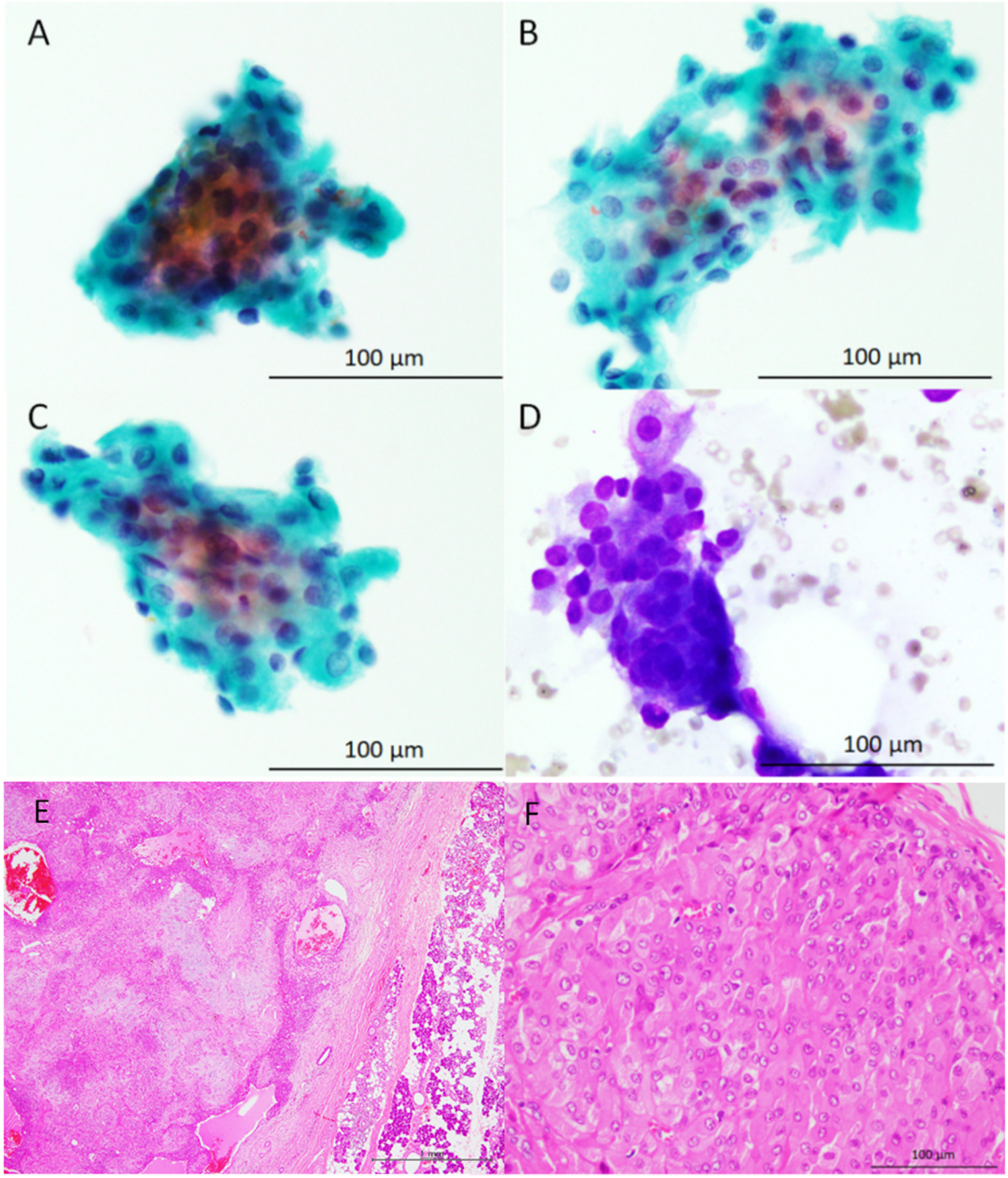

Figure 1. Cytological and histopathological features of the parotid gland tumour (patient 1). (A-D) Cytological features of the specimens of fine-needle aspiration. (A) A small cluster of oncocytic cells was present. (B) These oncocytic cells contained rich granular cytoplasm and relatively large nuclei. (C) These oncocytic cells had occasional nucleoli but the nuclear/cytoplasmic ratio was low. (D) Myxoid material with metachromasy was not present. (A-C) Papanicolaou and (D) Giemsa staining. (A-D) Magnification, x400; scale bar, 100 μm. (E and F) Histopathological features of the resected specimen. (E) A well-circumscribed tumour from the non-neoplastic parotid gland tissue. The tumour exhibited proliferation of neoplastic myoepithelial cells accompanied by myxoid material (haematoxylin and eosin staining; magnification, x40; scale bar, 1 mm). (F) Oncocytic neoplastic cells were present. The cells had rich eosinophilic granular cytoplasm containing relatively large round to oval nuclei with occasional nucleoli. Neither necrosis nor mitotic figures were observed (haematoxylin and eosin staining; magnification, x400; scale bar, 100 μm).

Histopathological features. The histopathological features of the resected parotid gland tumours are presented in Figs. 1-3 (Table I). The resected specimens demonstrated a relatively well-circumscribed tumour, and invasive neoplastic growth into the surrounding salivary gland tissue was not observed in any of the three tumour samples. The tumours were primarily composed of neoplastic myoepithelial cells containing small round-to-oval nuclei without rich eosinophilic granular cytoplasm or occasional ductal formations. Although cellular components without myxoid material were predominant in all tumours, these neoplastic myoepithelial cells blurred into myxoid or chondromyxoid material in at least some parts of

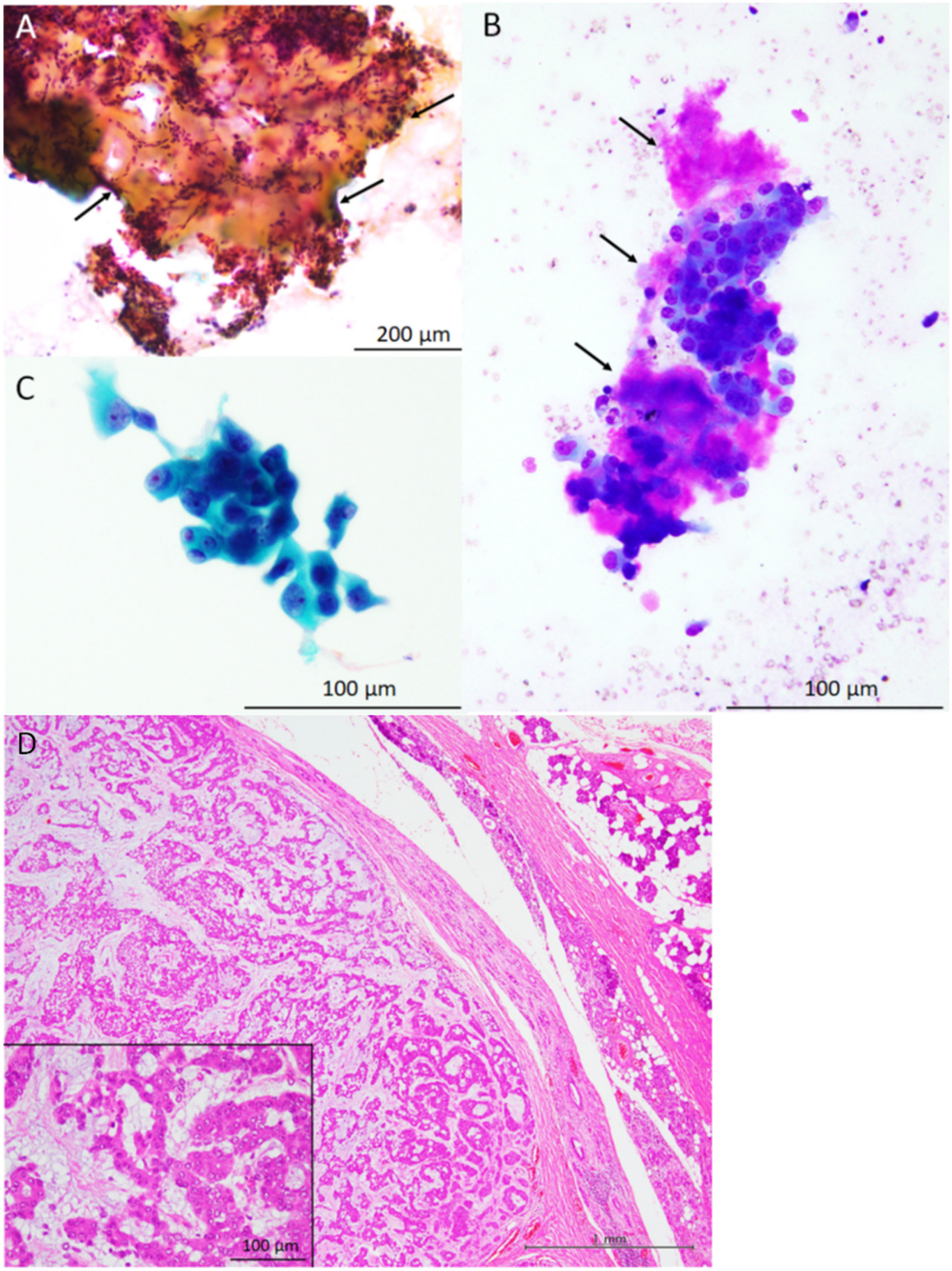

Figure 2. Cytological and histopathological features of the parotid gland tumour (patient 2). (A-C) Cytological features of the specimens of fine-needle aspiration. (A) Small and large clusters of oncocytic neoplastic cells were present. (B) The myxoid material showed metachromasy (arrows) around the clusters of oncocytic cells. (C) These oncocytic cells had granular cytoplasm and relatively large nuclei with nucleoli. (A and C) Papanicolaou and (B) Giemsa staining. (A) Magnification, x100; scale bar, 200 μm. (B and C) Magnification, x400; scale bar, 100 μm. (D) Histopathological features of the resected specimen. A well-circumscribed tumour from the non-neoplastic parotid gland tissue. The tumour exhibited proliferation of neoplastic myoepithelial cells within the myxoid material (haematoxylin and eosin staining; magnification, x40; scale bar, 1 mm). (Inset) The neoplastic myoepithelial cells exhibited an oncocytic nature (haematoxylin and eosin staining; magnification, x400; scale bar, 100 μm).

the tumours. Oncocytic cells containing rich granular eosinophilic cytoplasm and relatively large round-to-oval nuclei with nucleoli were observed in 30-60% of the tumours. Neither necrosis nor mitotic figures were observed in the oncocytic cells of any of the tumours. Based on these features, all patients were diagnosed with oncocytic PA.

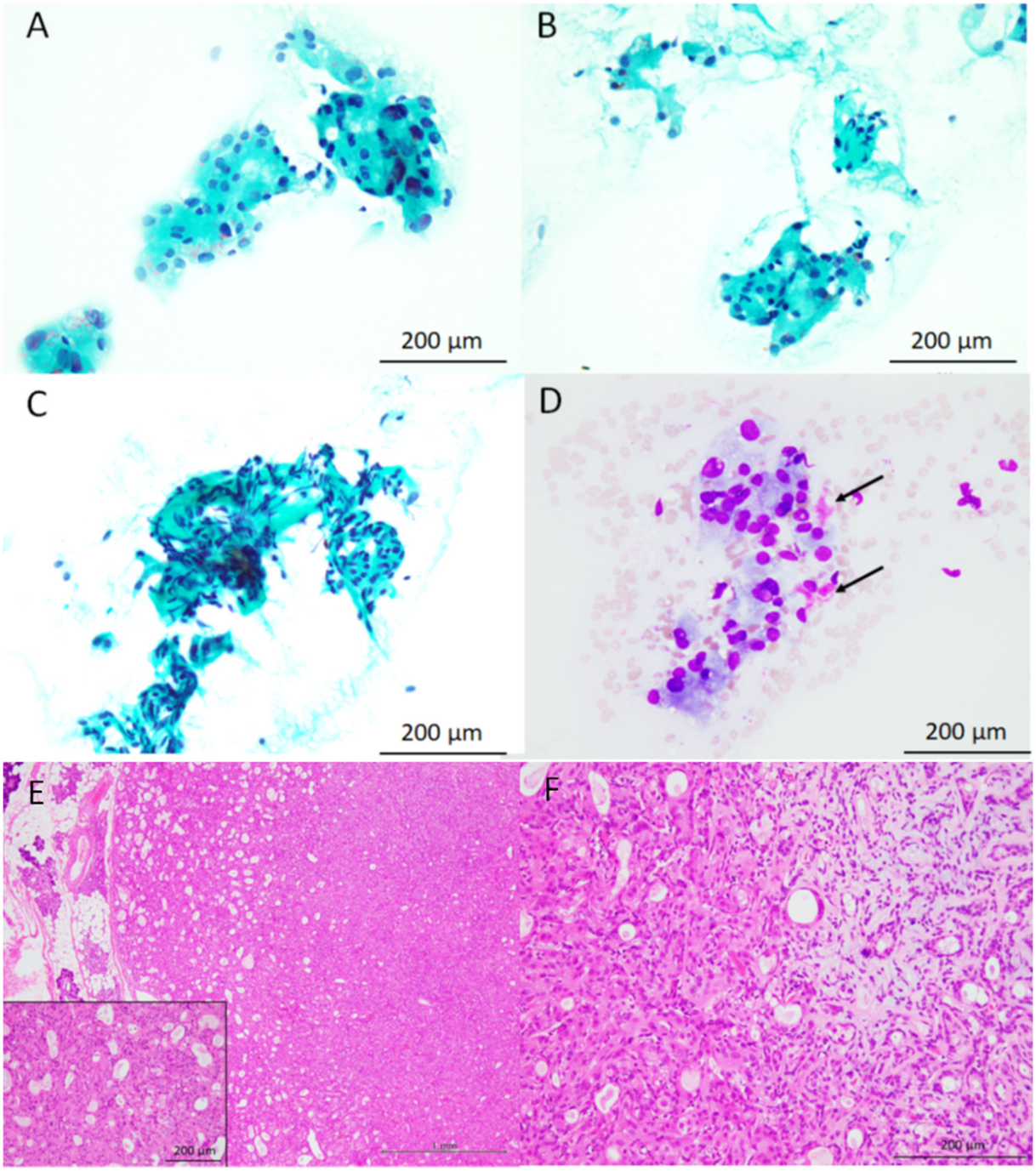

Figure 3. Cytological and histopathological features of the parotid gland tumour (patient 3). (A-D) Cytological features of the specimens of fine-needle aspiration. (A) Small clusters of oncocytic cells contained rich granular cytoplasm and relatively large nuclei. (B) These oncocytic cells had relatively large nuclei but the nuclear/cytoplasmic ratio was low. (C) A few conventional myoepithelial cell clusters. (D) Small amounts of metachromatic material were observed (arrows). (A-C) Papanicolaou and (D) Giemsa staining. (A-D) Magnification, x200; scale bar, 200 μm. (E) A well-circumscribed tumour from the non-neoplastic parotid gland tissue. The tumour exhibited proliferation of neoplastic oncocytic cells and occasional ductal formation. These oncocytic cells had rich granular cytoplasm containing relatively large nuclei with nucleoli [haematoxylin and eosin staining; magnification, x40 or x400 (inset); scale bar, 1 mm or 200 μm (inset)]. (F) Conventional pleomorphic adenoma component with biphasic proliferation of ductal and myoepithelial cells within the myxoid material (right side) and oncocytic component (left side; haematoxylin and eosin staining; magnification, x200; scale bar, 200 μm).

Immunohistochemical results. PLAG1 expression was noted in oncocytic cells of all three tumours (Fig. 4).

Discussion

In this study, we describe the cytological features of oncocytic PA. To the best of our knowledge, this is the first cytological case series of this rare PA variant. Various types of benign and malignant salivary gland tumours are known to have oncocytic cells (9,23). Therefore, the presence of oncocytic cells in cytological specimens from salivary gland FNA is a well-known phenomenon, and oncocytic lesions represent a subset of salivary gland tumours (18,23). Oncocytic cells are observed in Warthin's tumours, acinic cell carcinomas,

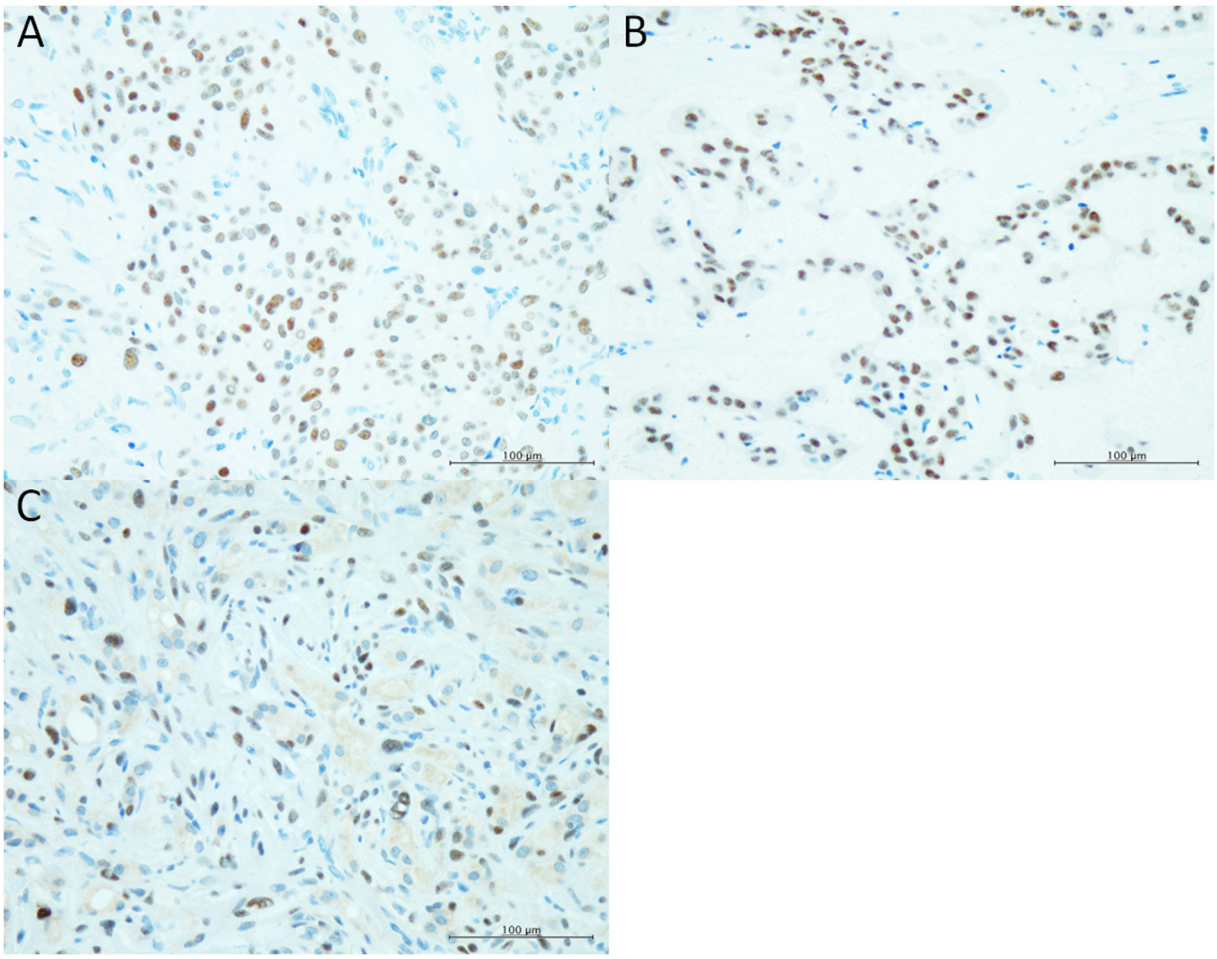

Figure 4. Immunohistochemistry of PLAG1. Oncocytic cells expressed PLAG1 in all three tumours. (A) Patient 1. (B) Patient 2. (C) Patient 3. Magnification, x400; scale bar, 100 μm. PLAG1, pleomorphic adenoma gene 1.

mucoepidermoid carcinomas, secretory carcinomas, and salivary duct carcinoma (SDC) (18,23). Although rare, oncocytic cells have been observed in PA (7-14). Skálová *et al* (7) reported nine cases of oncocytic PA and 11 cases of oncocytic myoepithelioma. The researchers described the histopathological features of oncocytic PA and highlighted the oncocytic changes in PA that could create challenges in the differential diagnosis of salivary gland tumours. In particular, oncocytic cells in PA are characterised by nuclear enlargement, hyperchromasia, and pleomorphism, leading to confusion about the malignant nature of the tumour (7). Although the incidence of oncocytic PA in the major salivary glands remains unknown (that of this cohort was 2.1%), a high frequency of oncocytic metaplasia (47.6% 10 of 21 patients) in intraoral PA has been reported (14). Di Palma *et al* (11) reported a case of oncocytic PA in which both conventional and oncocytic components showed the same genetic amplification, indicating the same clonal origin and subsequent acquisition of an oncocytic phenotype. Advances in molecular genetics have meant that most PA cases are now characterised by gene rearrangements resulting from gene fusions containing *PLAG1* or *high mobility group 2* (24). Some oncocytic PA harbour *PLAG1* fusion, and in some cases, initially diagnosed oncocytoma harbours *PLAG1* gene rearrangements, indicating that these tumours should be reclassified as pure-type oncocytic PA (25). In addition, a recent study demonstrated that pure oncocytic PA possesses a novel *PLAG1* fusion, such as *ZBTB47-AS1::PLAG1* (26). Accordingly, compared to conventional PA, oncocytic PA may have distinct molecular characteristics (25,26), and the molecular differences might be present between pure type oncocytic PA and PA with focal oncocytic cells (25,26). Disease concept and classification between PA and oncocytoma may be changing. In addition, the lack of the molecular tests examining *PLAG1* fusions was a limitation of the present report, although all of three oncocytic PA showed positive immunoreactivity for PLAG1. Molecular tests may be useful for diagnosis of salivary gland tumours showing oncocytic feature.

Only two cytological reports exist on oncocytic PA (15,16). The clinicopathological features of the previously reported oncocytic PA cases, as well as those of the present three patients, are summarised in Table I (15,16). In this study, all the tumours were located in the parotid glands. The median age of the patients was 51 years (range: 22-62 years). Four of the five cytological specimens contained myxoid material showing metachromasy with Giemsa staining in the background. Although the proportion of oncocytic cells in the cytological specimens was not available for one previously reported patient (16), most of the neoplastic cells present in the cytological specimens showed oncocytic morphology (n=4)

and conventional PA neoplastic cells were absent in two of the patients. The histopathological features of the resected tumour showed that oncocytic cells were predominant (ranging from 30 to >85%), and cytological FNA specimens were obtained from these regions. Avoiding malignant tumour overdiagnosis remains crucial during oncocytic PA cytodiagnosis. As described above, oncocytic cells have relatively large nuclei with nucleoli; thus, malignancy is commonly overdiagnosed. The initial cytological diagnoses for the present and previously reported oncocytic PA cases were malignant (CXPA) (patient 5), suspicious for malignancy (patients 2 and 3), undetermined (patient 1), and oncocytoma (patient 4) (15,16). Therefore, three of the five patients were suspected to have malignancies. To avoid overdiagnosis, the presence of oncocytic cells in PA specimens must be considered, and oncocytic PA must be included in the differential diagnosis of oncocytic lesions of the salivary gland (16,23).

MSRSGC has been widely used for the cytological diagnosis of salivary gland tumours (19-22). This system provides ROM and recommendations for therapeutic management for each tumour category (18). In four patients with oncocytic PA for whom information on MSRSGC was available, one, two, and one patient were classified as SUMP (IVB), suspicious for malignancy (V), and malignant (VI), respectively. This lesion should be categorised as SUMP (oncocytic/oncocytoid neoplasm) (16).

Cytological differential diagnostic considerations for oncocytic PA include various types of benign and malignant salivary gland tumours with oncocytic features (23). The most important cytological differential diagnosis is CXPA because myxoid material showing metachromasy in the background suggests the presence of PA and the presence of oncocytic neoplastic cells with large nuclei and occasional nucleoli, which lead to the suspicion of carcinoma cells. CXPA is defined as a carcinoma that develops from primary or recurrent PA and accounts for 12% of all salivary gland malignancies (27). Although various histological subtypes of carcinoma occur as components in CXPA, SDC, a common high-grade carcinoma of the salivary gland, is the most frequent (27). The characteristic cytological features of SDC are the presence of small and large epithelial cell clusters in a necrotic background. These neoplastic cells have large round to oval nuclei with conspicuous nucleoli and a relatively rich eosinophilic cytoplasm (28,29). In a review of the cytological features of CXPA, both carcinoma and PA components were noted in eight out of ten cytological specimens that can be cytodiagnosed as CXPA (28). Thus, careful observation enables the detection of carcinoma components, even in specimens with small amounts of carcinoma components or when carcinoma cells are intermingled within the PA component (28). These cytological features partially resemble those of oncocytic PA in the present series. Two of three tumours of the present series were cytodiagnosed as suspected for malignancy (especially CXPA), because the most common lesion containing rich eosinophilic cytoplasm and large nuclei in the salivary gland tumour is SDC. The most important differential diagnostic feature is the presence of necrotic material in CXPA and the absence of necrosis in oncocytic PA (15,16,28). Although oncocytic cells in PA have relatively large nuclei with occasional nucleoli, typical SDC shows high-grade nuclear atypia (28,29). Thus, the degree of nuclear atypia and the necrosis status allows for differential diagnosis.

Immunohistochemical staining for PLAG1 may be useful for diagnosing oncocytic PA (both pure oncocytic PA and PA with focal oncocytic metaplasia) (25). In the present series, all of three oncocytic PA showed positive immunoreactivity for PLAG1. Moreover, the usefulness of immunocytochemical staining for PLAG1 has been reported in cytological specimens categorised as SUMP (30). Although SDC, a carcinoma component of CXPA, also exhibits PLAG1 expression, other neoplastic lesions showing oncocytic features, such as Warthin's tumour, mucoepidermoid carcinoma, acinic cell carcinoma, and secretory carcinoma, do not present with PLAG1 positivity (24). Thus, immunocytochemical analysis of PLAG1 in oncocytic cells may be useful for detecting the origin of PA.

In conclusion, we described the cytological features of a series of cases of oncocytic PA in the salivary gland. Although rare, oncocytic cells may be present in cytological specimens of PA. These oncocytic cells have relatively large nuclei with occasional nucleoli; thus, a carcinoma overdiagnosis, particularly CXPA, is common. The absence of high-grade nuclear atypia and necrotic material is an important diagnostic criterion for the differential oncocytic PA diagnosis, and cytological specimens with atypical oncocytic cells in PA should be categorised as SUMP.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

NK and MI conceived the study. NK, MI, MO, HO, MT, KA, IK, YN, MU, CD, SO, RT, TT, SIH and YH analysed the cytological and/or clinicopathological data. NK and MI prepared the figures. NK and MI wrote the original draft and edited the draft. NK and MI confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with the tenets of the Declaration of Helsinki, and the study protocol was approved by the Institutional Review Board of Osaka Medical and Pharmaceutical University (protocol no. 2023-073; Takatsuki, Japan). All data were anonymised. The Institutional Review Board waived the requirement for informed consent due to the retrospective study design with no risk of patient identity exposure. In addition, the present study did not include children.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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