Chapter 6
Suspicious for Malignancy

Esther Diana Rossi, Andrew S. Field, Syed Z. Ali, Ashish Chandra, Yun Gong, Zahra Maleki, Bo Ping, and He Wang

General Background

The categories "Atypia of Undetermined Significance (AUS)," "Neoplasm: Salivary Gland Neoplasm of Uncertain Malignant Potential (SUMP)," and "Suspicious for Malignancy (SM)" represent indeterminate diagnostic categories in the Milan System [1]. They are used to stratify the risk of malignancy (ROM) and to inform the treating clinician that a particular specimen cannot be placed into a more specific benign or malignant diagnostic category due to diagnostic limitations such as sparse cellularity or various specimen artifacts (see Chaps. 4 and 5). The SM category is a traditional diagnostic category used in nearly all cytology reporting systems and, as such, its characteristics are well known to practicing cytologists [2–7]. The purpose of separating SM from the Malignant category is to preserve the high

Esther Diana Rossi and Andrew Field contributed equally to this work.

E.D. Rossi
Unita' Operativa Istopatologia e Citodiagnostica, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy
e-mail: esther.rossi@policlinicogemelli.it

A.S. Field (✉)
Anatomical Pathology, Notre Dame University Medical School and St Vincent's Hospital, Sydney, NSW, Australia
e-mail: Andrew.field@svha.org.au

S.Z. Ali • Z. Maleki
Department of Pathology, The Johns Hopkins Hospital, Baltimore, MD, USA
e-mail: sali@jhmi.edu; Zmaleki1@jhmi.edu

A. Chandra
Cellular Pathology, Guy's and St Thomas' NHS Foundation Trust, London, UK
e-mail: ashish.chandra@gstt.nhs.uk

W.C. Faquin et al. (eds.), *The Milan System for Reporting Salivary Gland Cytopathology*, https://doi.org/10.1007/978-3-319-71285-7_6

positive predictive value (PPV) of a fine-needle aspiration (FNA) classified as Malignant while at the same time offering a diagnostic option with a relatively high ROM for those FNAs where the cytomorphologic criteria fall short in quantity and/or quality for a Malignant diagnosis [8–16]. In the Milan System, the ROM for the SM category approaches 60% [1]. With the growing availability of immunohistochemical and molecular markers for salivary gland tumors (see Chap. 8), a subset of FNAs classified as SM may benefit from the application of ancillary testing to yield a more specific interpretation.

Definition

A salivary gland FNA is classified as SM when some, but not all the criteria for a specific diagnosis of malignancy are present, and yet the overall cytologic features are suggestive of malignancy.

Cytologic Criteria

When making a diagnosis of SM, the FNA should be described as suspicious for a primary salivary gland malignancy, or suspicious for a metastasis, or lymphoma [8–12]. A significant proportion of SM cases will be suboptimal samples of a high-grade malignancy. Aspects of a salivary gland FNA leading to an interpretation of SM include:

- Markedly atypical cells with poor smear preparation, poor cell preservation, fixation artifact, or obscuring inflammation and blood (Figs. 6.1 and 6.2)
- Presence of limited cytologic features of a specific malignant lesion (e.g., adenoid cystic carcinoma, mucoepidermoid carcinoma, and acinic cell carcinoma) in an otherwise sparsely cellular aspirate (Figs. 6.3, 6.4, and 6.5)
- Presence of markedly atypical and/or suspicious cytologic features in a subset of cells but admixed with features of a benign salivary gland lesion (Fig. 6.6).

Y. Gong
Department of Pathology, University of Texas MD Anderson Cancer Center, Houston, TX, USA
e-mail: yungong@mdanderson.org

B. Ping
Department of Pathology, Fudan University Shanghai Cancer Hospital, Shanghai, People's Republic of China
e-mail: bping2007@163.com

H. Wang
Pathology and Laboratory Medicine, Temple University Hospital, Philadelphia, PA, USA
e-mail: he.wang@tuhs.temple.edu

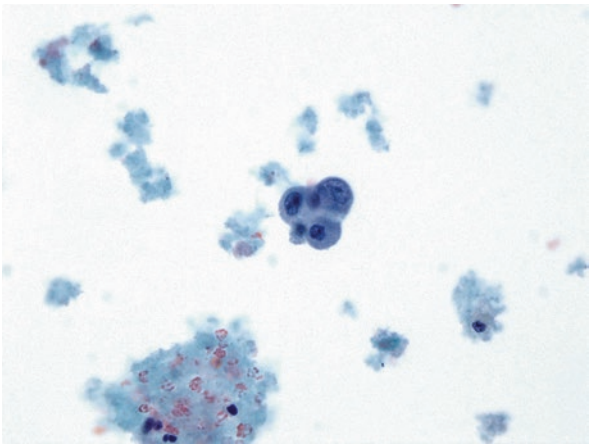

Fig. 6.1 Suspicious for Malignancy. The smear shows rare markedly atypical cells suggestive of carcinoma, but the classification is limited by scant cellularity (smear, Papanicolaou stain)

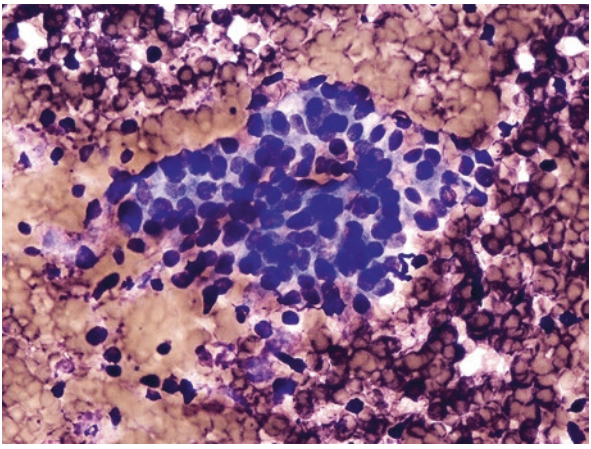

Fig. 6.2 Suspicious for Malignancy. The smear contains markedly atypical cells suspicious for high-grade carcinoma, but with obscuring blood limiting the assessment (smear, Romanowsky stain)

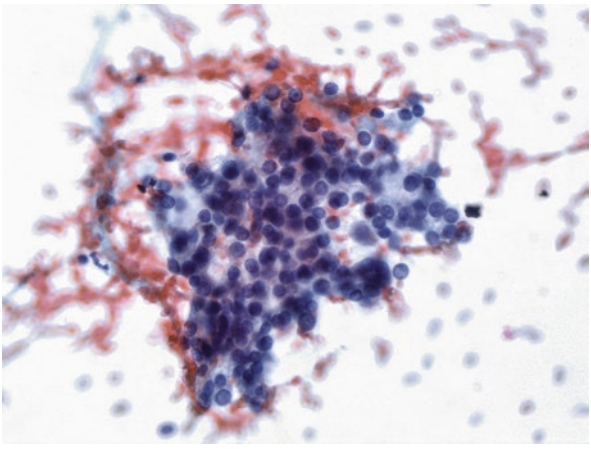

Fig. 6.3 Suspicious for Malignancy. The smear shows a group of epithelial cells suggestive of acinic cell carcinoma, but hypocellularity and background blood in the absence of ancillary studies limits the evaluation (smear, Papanicolaou stain)

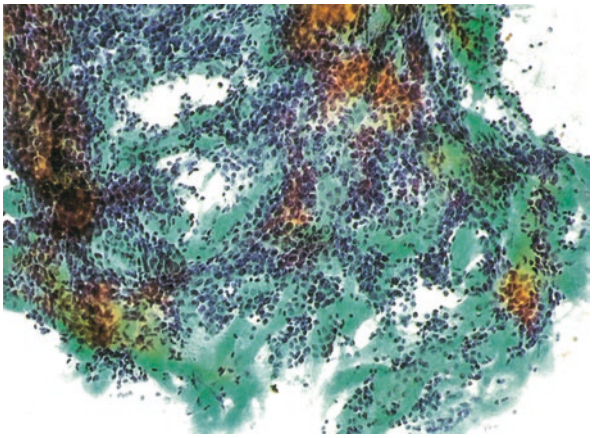

Fig. 6.4 Suspicious for Malignancy. This smear is composed of basaloid cells and abundant matrix spheres with a pattern suspicious for adenoid cystic carcinoma (smear, Papanicolaou stain)

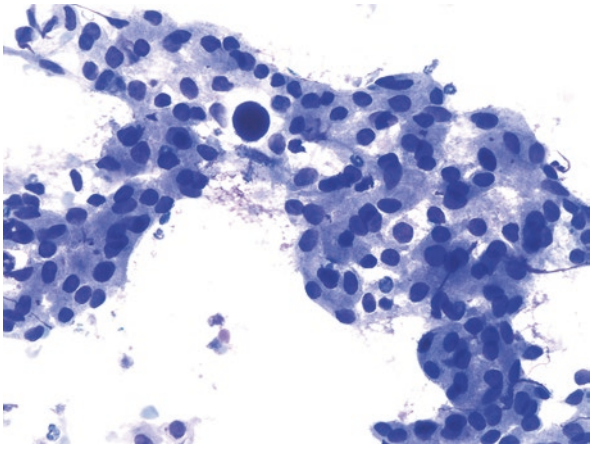

Fig. 6.5 Suspicious for Malignancy. The smear consists of epithelial cells with epidermoid features, suggestive of mucoepidermoid carcinoma (smear, Romanowsky stain)

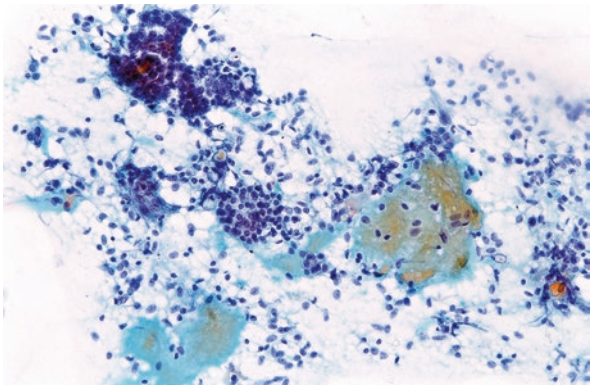

Fig. 6.6 Suspicious for Malignancy. The smear shows presence of markedly atypical (*upper left*) cytologic features in a subset of cells admixed with features of pleomorphic adenoma (smear, Papanicolaou stain)

Atypical features can include prominent nucleoli or macronucleoli, anisonucleosis, increased nuclear to cytoplasmic ratio, nuclear molding, prominent nuclear pleomorphism, atypical mitosis, and clumped, coarse chromatin (Fig. 6.7).

- Scant sample with atypical features suggestive of a neuroendocrine neoplasm (Fig. 6.8)

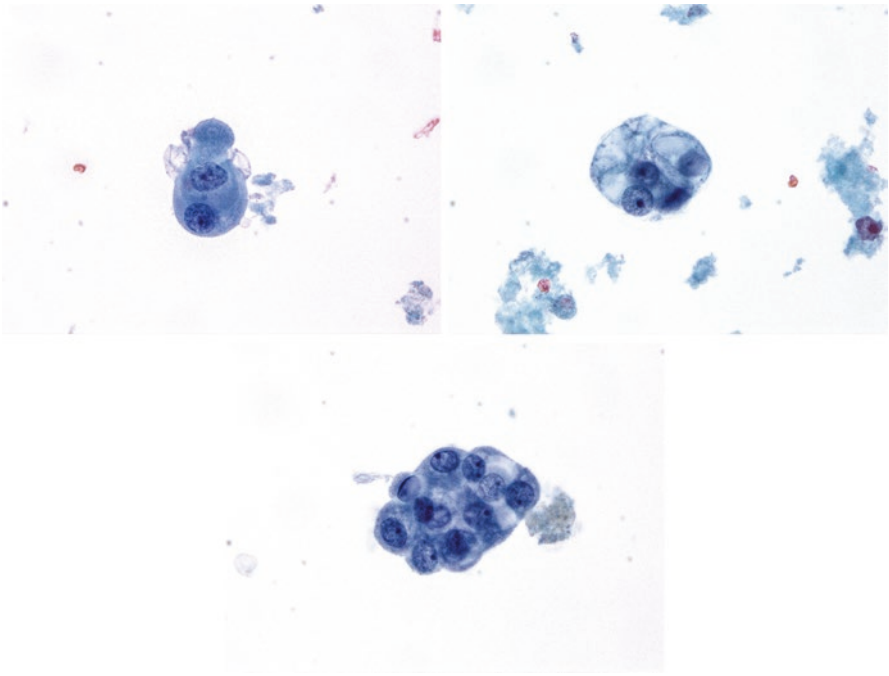

Fig. 6.7 Suspicious for Malignancy. This aspirate is hypocellular but contains occasional small groups of markedly atypical cells suspicious for carcinoma. The corresponding resection showed a high-grade mucoepidermoid carcinoma (smear, Papanicolaou stain)

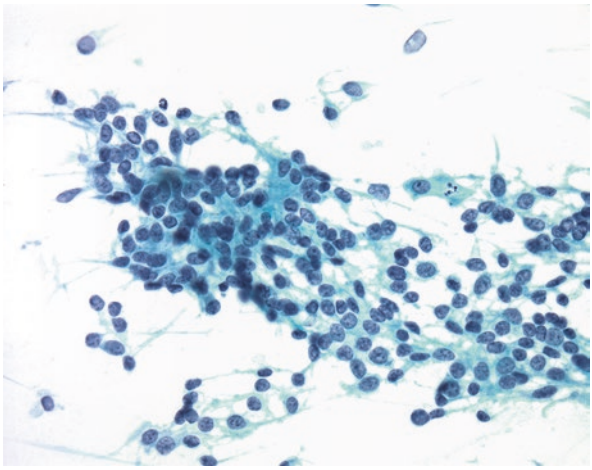

Fig. 6.8 Suspicious for Malignancy. This smear shows neoplastic cells containing nuclei with "salt and pepper" chromatin suggestive of neuroendocrine differentiation (smear, Papanicolaou stain)

A differential diagnosis of lymphoma is usually considered in salivary gland aspirates with a prominent population of lymphocytes or atypical lymphoid cells with microscopic fragments of lymphocyte cytoplasm ("lymphoglandular bodies") in the background [17, 18]. Immunophenotyping, usually by flow cytometry, is key to making a diagnosis of most lymphomas in cytologic specimens. Thorough clinical correlation is also essential. Successful subclassification of lymphoma may require performance of ancillary immunohistochemical and molecular studies. Many of the aspirates of lymphoma classified as SM lack sufficient material for the performance of these ancillary studies [17, 18]. A detailed cytology review of lymphoma diagnosis is beyond the scope of this atlas, but some of the cytomorphologic features suggestive of a lymphoma include:

- A population of enlarged atypical lymphoid cells as seen in large cell lymphomas (Fig. 6.9)
- A monomorphic lymphoid population. This may be made up of small/intermediate lymphocytes as in intermediate grade follicular lymphoma (Fig. 6.10), or showing angulated, indented nuclei resembling centrocytes suggesting mantle cell lymphoma, or small lymphocytes with round nuclei and coarse chromatin suggesting small lymphocytic lymphoma
- A heterogeneous lymphoid population with atypical forms (Fig. 6.11). Extranodal marginal zone lymphomas (ENMZL) are especially characterized by a heterogeneous cell population including small to intermediate size centrocyte-like cells, and a smaller number of larger lymphoid cells, plasmacytoid cells, tingible body macrophages, dendritic cells, and plasma cells.

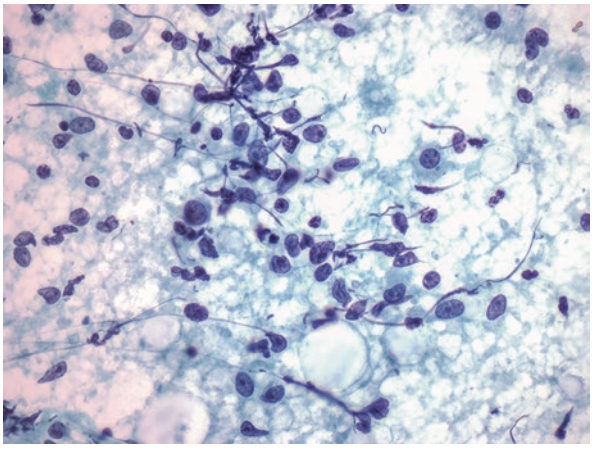

Fig. 6.9 Suspicious for Malignancy. This smear shows a population of enlarged atypical lymphoid cells suspicious for a large cell lymphoma (smear, Papanicolaou stain)

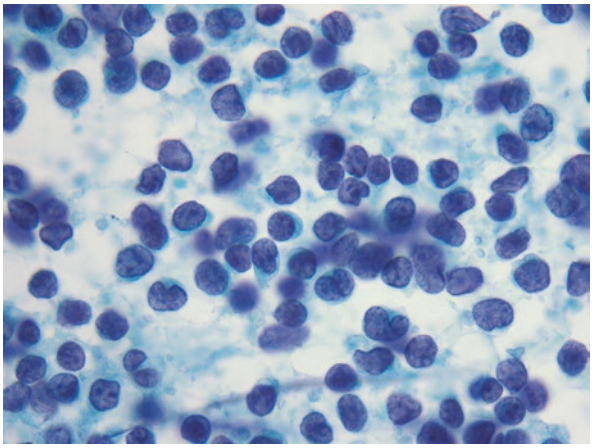

Fig. 6.10 Suspicious for Malignancy. This aspirate shows a monotonous population of intermediate-size lymphocytes that, based upon cytomorphology alone, are highly suspicious for lymphoma. Additional ancillary studies including immunophenotyping are needed for classification (smear, Papanicolaou stain)

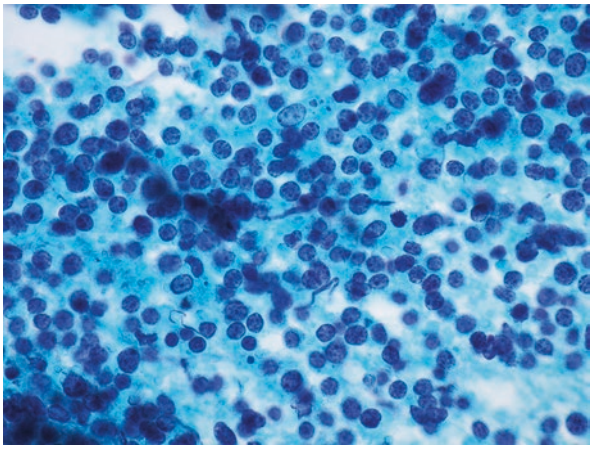

Fig. 6.11 Suspicious for Malignancy. This smear shows a polymorphous pattern with a predominance of intermediate-size lymphoid cells as can be seen in marginal zone lymphomas. Ancillary studies are needed for further classification (smear, Papanicolaou stain)

Explanatory Notes

A diagnosis of SM can be made in aspirates showing focal marked cellular atypia in a less than optimal specimen. Once significant atypia, suggesting malignancy, is identified in an FNA that is hypocellular or poorly prepared, the case is no longer insufficient or "Non-Diagnostic." SM also usually indicates that the cytology is characterized by a higher degree of atypia than in those aspirates in the AUS and SUMP categories, thus highly suggestive of a malignant lesion. SM should not be used for cases where the overall cytomorphological features are better classified as AUS or SUMP. The latter are associated with a significantly lower ROM than cases classified as SM. The cytomorphological stratification of AUS, SUMP, and SM can be subtle and in some cases subjective, but careful scrutiny of the cytomorphological features and proper application of ancillary techniques will aid in accurate

classification. In some cases, the diagnosis of "Suspicious for Malignancy" may be upgraded to "Malignant" once the results of any ancillary studies become available. Whenever rapid on-site evaluation (ROSE) is offered, it can be used to improve the quality and quantity of the FNA specimen, and assist in triaging material for additional diagnostic studies.

A majority of salivary gland FNAs classified as SM will be samples of high-grade cancers that have some limiting factors precluding a definitive diagnosis of malignancy. A subset of cases will be lower-grade salivary gland cancers that exhibit many of the characteristic cytologic features of a particular salivary gland cancer, but for qualitative or quantitative reasons are not sufficient to be diagnostic (Fig. 6.12). Most commonly, aspirates of low-grade mucoepidermoid carcinoma, acinic cell carcinoma, and adenoid cystic carcinoma will fall into the latter subset. Other tumors such as aspirates of neuroendocrine carcinoma, which are rare in the salivary gland, are usually diagnostic of malignancy provided that adequate material is available for ancillary studies. The most common form of neuroendocrine carcinoma in the salivary gland is poorly differentiated neuroendocrine carcinoma with Merkel cell-like features, and by cytomorphology alone it would typically be interpreted as malignant unless it were a compromised specimen.

Salivary gland aspirates containing a prominent lymphoid population will require ancillary studies for a definitive diagnosis of lymphoma. Otherwise, classification of the aspirate as SM can be used for cases where there is a cytologic pattern suggesting lymphoma such as the presence of large atypical lymphoid cells or a monomorphic lymphoid population. Most often, there will be a heterogeneous lymphoid population, and the differential diagnosis will include a benign process such as reactive lymphoid hyperplasia, chronic sialadenitis, or Sjogren's syndrome. Occasionally, such cases can exhibit sufficient atypical cytomorphologic and clinical features as to be suspicious for lymphoma, but flow cytometry or other methods of immunophenotypic analysis are essential to ultimately rule in or rule out lymphoma. If the

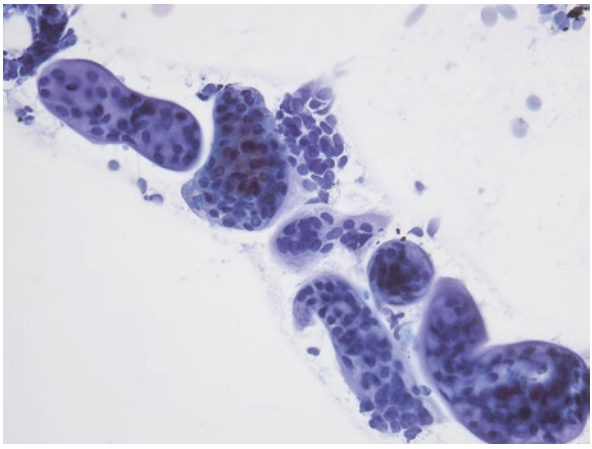

Fig. 6.12 Suspicious for Malignancy. This smear shows cytologic features that are highly suspicious for adenoid cystic carcinoma, but the specimen is limited to a single Papanicolaou-stained smear (smear, Papanicolaou stain)

FNA has not been submitted for flow cytometry, repeat FNA with flow is the best approach, and if there is local expertise, core biopsy can be added. Correlation with hematopathology is recommended, and in some cases, surgical excision of the lesion will be indicated for definitive diagnosis and subclassification for those lesions that are lymphoma. While rarely involving the salivary glands or intraparotid lymph nodes, classic Hodgkin lymphoma has distinctive cytomorphologic features that would lead to a diagnosis of at least "Suspicious for Hodgkin lymphoma" in most cases. Flow cytometry would generally not be useful for confirming the diagnosis of Hodgkin lymphoma, but material for other ancillary studies would be indicated; excisional biopsy may be needed for a definitive diagnosis.

Clinical Management

The cytologic diagnosis of SM is not equivalent to "Malignant," even though it is suggestive of a malignant lesion and the risk of malignancy is high. It cannot be used alone as a basis for radical surgery, chemotherapy, or radiotherapy (see Chap. 9). In response to a diagnosis of SM, consideration should be given as to whether or not obtaining additional material by repeat FNA, core biopsy, open biopsy, or surgical excision would be most useful. For cases with repeat FNA, every effort should be made to obtain adequate material for any ancillary studies that would be indicated. Clinical and radiologic correlations are of course important, and when surgery is performed, intraoperative frozen section can be considered in appropriate cases.

Sample Reports

Example 1:
Satisfactory for evaluation
SUSPICIOUS FOR MALIGNANCY
Rare markedly atypical cells, suspicious for high-grade carcinoma.

Example 2:
Satisfactory for evaluation
SUSPICIOUS FOR MALIGNANCY
Suspicious for high-grade mucoepidermoid carcinoma/adenoid cystic carcinoma/salivary duct carcinoma.

Example 3:
Evaluation limited by scant cellularity
SUSPICIOUS FOR MALIGNANCY
Atypical cells in a mucinous background, suspicious for low-grade mucoepidermoid carcinoma.

Example 4:
Satisfactory for evaluation
SUSPICIOUS FOR MALIGNANCY
Rare large atypical lymphocytes, suspicious for non-Hodgkin lymphoma. See note.
Note: Further evaluation using immunophenotyping studies by flow cytometry or immunochemistry in a repeat FNA or tissue sample is recommended.

Example 5:
Satisfactory for evaluation
SUSPICIOUS FOR MALIGNANCY
Monomorphic population of atypical small lymphoid cells, suspicious for non-Hodgkin lymphoma. See note.
Note: Additional tissue sampling either by repeat FNA or tissue biopsy is recommended for further evaluation with ancillary studies including flow cytometry.

Example 6:
Evaluation limited by scant well-preserved cells
SUSPICIOUS FOR MALIGNANCY
Cyst contents with occasional atypical squamous cells and dyskeratotic cells, suspicious for metastatic keratinizing squamous cell carcinoma.

References

1. Rossi ED, Faquin WC, Baloch Z, Barkan GA, Foschini MP, Pusztaszeri M, et al. The Milan system for reporting salivary gland cytopathology: analysis and suggestions of initial survey. Cancer Cytopathol. 2017;125(10):757–66. https://doi.org/10.1002/cncy.21898.
2. Contucci AM, Corina L, Sergi B, Fadda G, Paludetti G. Correlation between fine needle aspiration biopsy and histologic findings in parotid masses. Personal experience. Acta Otorhinolaryngol Ital. 2003;23(4):314–8.
3. Griffith CC, Pai RK, Schneider F, Duvvuri U, Ferris RL, Johnson JT, Seethala RR. Salivary gland tumor fine needle aspiration cytology. A proposal for a risk stratification classification. Am J Clin Pathol. 2015;143(6):839–53.
4. Hughes JH, Volk EE, Wilbur DC, Cytopathology Resource Committee, College of American Pathologists. Pitfalls in salivary gland fine needle aspiration cytology: lessons from the college of American pathologists interlaboratory comparison program in nongynaecologic cytology. Arch Pathol Lab Med. 2005;129(1):26–31.
5. Jain R, Gupta R, Kudesia M, Singh S. Fine needle aspiration cytology in diagnosis of salivary gland lesions: a study with histologic comparison. Cytojournal. 2013;10:5.
6. Mairembam P, Jay A, Beale T, Morley S, Vaz F, Kalavrezos N, Kocjan G. Salivary gland FNA cytology: role as a triage tool and an approach to pitfalls in cytomorphology. Cytopathology. 2016;27(2):91–6.
7. Rossi ED, Wong LQ, Bizzarro T, Petrone G, Mule A, Fadda G, Baloch ZM. The impact of fine needle aspiration cytology in the management of salivary gland lesions: institutional experiences leading to a risk based classification scheme. Cancer Cytopathol. 2016;124(6):388–96.
8. Brennan PA, Davies B, Poller D, Mead Z, Bayne D, Puxeddu R, Oeppen RS. Fine needle aspiration cytology (FNAC) of salivary gland tumours: repeat aspiration provides further information in cases with an unclear initial cytological diagnosis. Br J Oral Maxillofac Surg. 2010;48(1):26–9.
9. Wei S, Layfield LJ, LiVolsi VA, Montone KT, Baloch ZW. Reporting of fine needle aspiration (FNA) specimens of salivary gland lesions: a comprehensive review. Diagn Cytopathol. 2017;45(9):820–7.
10. Colella G, Cannavale R, Flamminio F, Foschini MP. Fine-needle aspiration cytology of salivary gland lesions: a systematic review. J Oral Maxillofac Surg. 2010;68(9):2146–53.
11. Tyagi R, Dey P. Diagnostic problems of salivary gland tumors. Diagn Cytopathol. 2015;43(6):495–509.
12. Wang H, Fundakowski C, Khurana JS, Jhala N. Fine-needle aspiration biopsy of salivary gland lesions. Arch Pathol Lab Med. 2015;139(12):1491–7.
13. Darvishian F, Lin O. Myoepithelial cell-rich neoplasms: cytologic features of benign and malignant lesions. Cancer Cytopathol. 2004;102(6):355–61.
14. Chen L, Ray N, He H, Hoschar A. Cytopathologic analysis of stroma-poor salivary gland epithelial/myoepithelial neoplasms on fine needle aspiration. Acta Cytol. 2012;56(1):25–33.
15. Layfield LJ, Glasgow BJ. Diagnosis of salivary gland tumors by fine needle aspiration cytology: a review of clinical utility and pitfalls. Diagn Cytopathol. 1991;7(3):267–72.
16. Singh Nanda KD, Mehta A, Nanda J. Fine-needle aspiration cytology: a reliable tool in the diagnosis of salivary gland lesions. J Oral Pathol Med. 2012;41(1):106–12.
17. Turner MD. Salivary gland disease in Sjögren's syndrome: sialoadenitis to lymphoma. Oral Maxillofac Surg Clin North Am. 2014;26(1):75–81.
18. Field AS, Geddie WR. Cytohistology of Lymph Nodes and Spleen, Cambridge University Press, Cambridge, United Kingdom, 2014.