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Cytological evaluation of lymphoepithelial lesions of the major salivary glands with special reference to lymphoepithelial sialadenitis: A clinicopathological study

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ABSTRACT

Background: Fine needle aspiration cytology (FNAC) is an accurate, reliable, minimally invasive, and cost-effective procedure for pre-operative evaluation of salivary gland lesions. Salivary glands are host to a wide range of pathological conditions ranging from reactive, inflammatory, and cystic conditions to neoplastic lesions. In comparison to the epithelial lesions, salivary gland lymphoepithelial lesions (LELs) are rare. Cytological evaluation of the salivary gland LELs was described as case reports in few literatures. **Aims and Objectives:** The current study aimed to discuss cytological features of the LELs of the salivary gland elaborately. **Materials and Methods:** The study was conducted over a period of 5 years in which a total of 720 salivary gland FNAC samples along with their clinical presentations were studied. LELs were diagnosed in 36 cases. **Results:** Out of these lymphoepithelial cysts were diagnosed in 5 cases (13.88%), lymphoepithelial sialadenitis in 16 (44.44%), suggestive of lymphoepithelial carcinoma in 2 (5.5%), and lymphoepithelial sialadenitis with close differential diagnosis such as chronic sclerosing sialadenitis (7,19.44%), Warthin's tumor (4,10.11%), and low-grade lymphoma in rest of the cases (2,5.5%). **Conclusion:** LELs are rare lesions of the salivary gland characterized by lymphocyte infiltration into the salivary parenchyma with associated salivary ductal epithelial cell proliferation. These lesions include reactive non-neoplastic lesions to benign and malignant lesions whose clinical significance varies greatly among these lesions. Hence, careful history taking, clinical examination findings, and adequate sampling for cytological evaluation play pivotal role in a conclusive diagnosis preoperatively which leads to better patient management.

Key words: Fine needle aspiration cytology; Lymphoepithelial lesions; Lymphoepithelial sialadenitis; Salivary gland

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INTRODUCTION

Fine needle aspiration cytology (FNAC) is a reliable, minimally invasive, and cost-effective procedure for the evaluation of salivary gland pathologies.[1,2] For diagnostic evaluation of salivary gland pathologies, FNAC is the first and primary investigation before any surgical intervention. Out of all the head-and-neck neoplasms, salivary gland neoplasms account for 2–6.5% of it.[3]

In most of the literature, the cytological findings of epithelial lesions of the salivary glands were well elaborated whereas lymphoepithelial lesions (LELs) of the salivary glands were only described in few literature as case reports.

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Lymphocyte infiltrates in major salivary glands include a wide range of conditions starting with non-neoplastic/reactive (lymphoepithelial cyst and lymphoepithelial sialadenitis [LESA]) and benign tumors (Warthin's tumor) to malignant tumors (lymphoepithelial carcinoma [LEC] and marginal zone lymphoma).

Due to the close relationship between the lymphoid tissue and salivary gland parenchyma, various reactive and neoplastic conditions affecting the lymphoid tissue produce salivary glands lesions.

Since the therapeutic implications of these lesions (reactive Vs malignant) vary considerably, FNAC plays an important role in establishing preoperative diagnosis and sometimes obviates unnecessary radical surgery in reactive lesion as compared to the malignant one.[1]

There were only few studies in the literature that demonstrated the role of FNAC in the diagnosis of lymphoid lesions of the salivary gland.[4-6]

Aims and objectives

In this study, we have described the LELs of the major salivary glands with a special discussion on LESA.

MATERIALS AND METHODS

Study design, duration, and place of study

This was a retrospective study conducted over a period of 5 years from January 2017 to January 2022 in a tertiary care hospital.

Patient selection

All the patients with clinical presentation of mass lesion of the major salivary glands were received in our department of Pathology for cytologic evaluation by FNAC.

Inclusion criteria

Out of 720 cases of major salivary gland mass lesions evaluated by FNAC, 36 cases diagnosed as LELs were included in this study.

Exclusion criteria

Lesions of minor salivary glands and cases which were diagnosed as benign/malignant tumor of epithelial origin were excluded from the study.

Relevant clinical data

Patient's age, sex, anatomical site and size of the salivary glands, duration, history of autoimmune disorder, and human immunodeficiency virus (HIV) infection were collected from the clinical records.

Patient consent

Consent was taken from all the individuals before the FNAC procedure.

Procedure

FNACs were done by 22 gauge needles and both air-dried and alcohol-fixed (Ethanol) smears were prepared. In the case of frank, fluid aspirates, first centrifugation was done in our cytology laboratory, and then, both air-dried and alcohol-fixed smears were prepared from the centrifuged deposits. The air-dried smears and ethanol-fixed smears were stained by Leishman/May Grünwald Giemsa and Papanicolaou stains, respectively.

Evaluation of the smears

All the cytological smears diagnosed as LELs were reevaluated by two independent cytopathologists and final diagnosis with differential diagnosis (D/D) as applicable was made.

Statistical analysis

All the values were represented in MS Excel spreadsheet as number (n) and percentage (%). Software version IBM SPSS 20.0 was used for statistical analysis.

RESULTS

A total of 720 cases of salivary gland lesions were evaluated out of which 642 (89.16%) cases were adequate for evaluation. Out of 642 cases of salivary gland FNAC, LELs were diagnosed in 36 cases (9.35%) (Table 1).

The most common age group affected by LELs was between 51 and 70 years of age (n=16, 44.44%). Out of the major salivary glands, parotid glands were most commonly involved (80.55%) (Table 2).

Bilateral parotid enlargement was seen in 16 cases (44.44%) (Table 2). Clinical history of dry eye and dry mouth was found in 5 cases (13.88%). Serological evidence of autoimmune disorder and HIV enzyme-linked immunosorbent assay positivity was found in 9 (25%) and 3 (8.33%) cases, respectively (Table 3).

Out of the 36 cases, lymphoepithelial cysts were found in 5 cases (13.88%). LESA found in 16 cases (44.44%) (Table 1 and Figure 1), LESA with a D/D of chronic sclerosing sialadenitis in 7 cases (19.44%) (Table 1 and Figure 2), LESA with a D/D of Warthin's tumor in 4 cases (10.11%) (Figure 3), LEC in 2 cases (5.5%), and LESA with a D/D of low-grade lymphoma in 2 cases (5.5%). Various spectrums of other cytological findings such as exuberant ductular proliferation, squamous metaplasia, and oncocytic changes were also seen.

Table 1: FNAC smear adequacy and incidence of lymphoepithelial lesions

Total number of salivary gland FNAC smears evaluated=426		
Smears examined	**Number (n)**	**Percentage**
Adequate for evaluation	385	90.37
Inadequate for evaluation	41	9.62
Total number of cases diagnosed as lymphoepithelial lesion	36	9.35

FNAC: Fine needle aspiration cytology

Table 2: Clinical presentation of the patients diagnosed as lymphoepithelial lesions of the major salivary glands n=36

Parameters	**Numbers (n)**	**Percentage**
a) Age		
11–30 years	2	5.5
31–50 years	13	36.11
51–70 years	16	44.44
>70 years	5	13.88
b) Sex		
Male	13	96.11
Female	23	63.88
c) Site		
Unilateral parotid gland	13	36.11
Bilateral parotid gland	16	44.44
Submandibular gland	7	19.44
d) Radiological findings		
Available	11	30.55
Not available	25	69.44

Table 3: Clinical history of the patients, n=36

Parameters	**Number (n)**	**Percentage**
1) History of dry eye and dry mouth	5	13.88
2) ELISA positivity for HIV	3	8.33
3) Serological evidence of autoimmunity	9	25
4) No suggestive history	19	52.77

ELISA: Enzyme-linked immunosorbent assay, HIV: Human immunodeficiency virus

DISCUSSION

LELs are rare lesions of the salivary glands characterized by lymphocytic infiltration associated with epithelial proliferation.[7]

Lymphocytic infiltration in the salivary gland causing LELs includes a wide spectrum of diseases which include reactive/benign lymphoepithelial cyst, LESA, and malignant LEC with a close (D/D) of low-grade lymphoma and Warthin's tumor.

Although tissue diagnosis still remains as the gold standard for the evaluation of salivary gland lesions, FNAC plays an important role in the evaluation of these lesions.

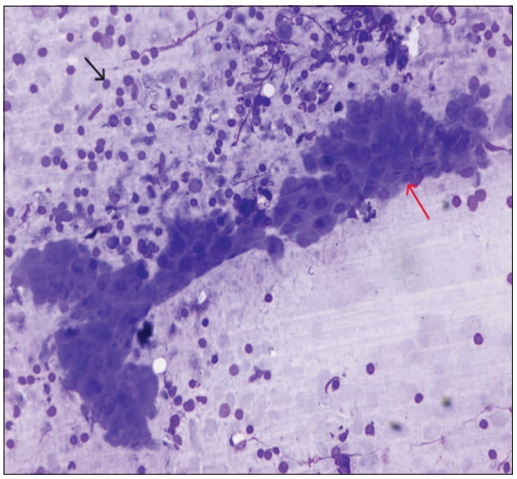

Figure 1: Cytosmear showing salivary gland ductal epithelial cells (red arrow) in a background of numerous reactive lymphoid cells (black arrow) in case of lymphoepithelial sialadenitis (Leishman Giemsa stain, 400×)

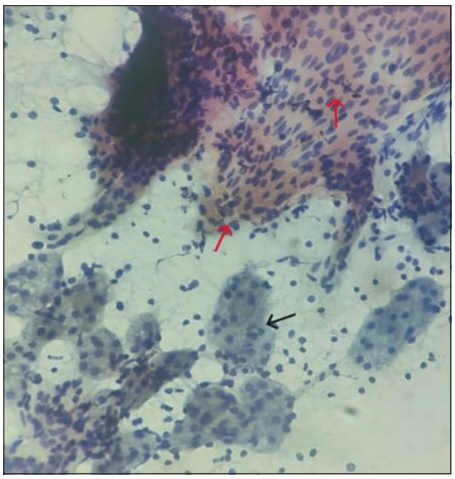

Figure 2: Cytosmear showing squamous metaplasia of salivary ductal epithelial cells (red arrow) and lymphocytes in the background and acini (black arrow) (lymphoepithelial sialadenitis with a differential diagnosis of chronic sclerosing sialadenitis) (Papanicolaou, 400×)

The primary role of FNAC is to distinguish reactive lesions from neoplastic lesions and further subtyping into malignant and benign lesions. This leads the surgeon to decide the type and extent of surgery in neoplastic lesions and at the same time, it prevents unnecessary surgery in cases of non-neoplastic/reactive lesions. In majority of the cases, aspirate obtained by salivary gland FNAC is adequate for evaluation to have a definitive/conclusive diagnosis as reported by Das et al.,[8] and Nguansangiam et al.[9]

In our study, out of 720 cases in 642 cases (89.16%), aspirated materials were adequate for evaluation and in 10.83 % of cases, aspirate was inadequate for evaluation. This was similar to the study by Sandhu et al.,[10] in which

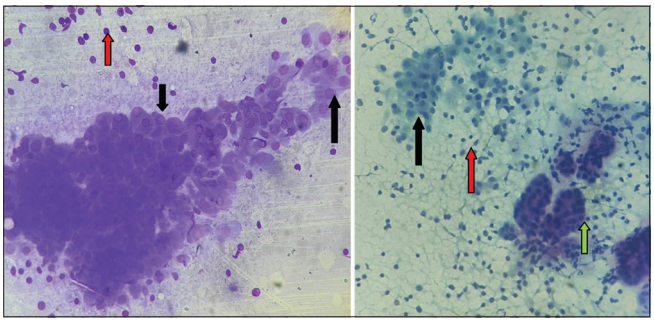

Figure 3: Cytosmear showing reactive lymphoid cells (red arrow), ductal epithelial cells with oncocytic change (black arrow), and salivary gland acini (green arrow) (lymphoepithelial sialadenitis with a differential diagnosis of Warthin's tumor) (Leishman stain, 400×) (inset, Papanicolaou stain, 400×)

88.2% of cases were adequate for evaluation and 11.7% were inadequate for evaluation.

Out of these aspirates, LELs were identified in 36 cases (Table 1).

Histogenesis of LELs

During fetal development, the parenchyma of the parotid gland is colonized by lymphocytes to form small lymphoid aggregates within the glandular tissue, with an average of 5 to 10 lymphocytes present in adult life.[5]

LELs were encountered only rarely in salivary gland lesion FNAC. LELs most likely occurred in adults with approximately 60–80% of cases affecting females.[5]

In our study, the various LELs diagnosed by FNAC were as follows: Lymphoepithelial cyst (n=5, 13.88%), LESA (n=16, 44.44%), and LEC (n=2, 5.5%) (Table 4) and LESA with a D/D of (i) chronic sclerosing sialadenitis (n=14, 19.44%), (ii) low-grade lymphoma where predominantly lymphoid component was aspirated (n=4,5.5%), and (iii) Warthin's tumor in which florid oncocytic cells were seen (n=8, 10.11%) (Table 4).

Lymphoepithelial cyst

The term "Lymphoepithelial cyst" was introduced by Bernier and Bhaskar and they defined it as solitary or multiple cysts within lymph nodes associated with salivary glands. Involvement of the parotid gland is seen infrequently.[11]

One of the typical characteristics of this lesion is that it is commonly seen in HIV-positive patients[12] with rare occurrence in non-HIV individuals[13] in which the possible source of infection could be chronic otitis media spreading to the intraparotid lymph node.

Table 4: Different types of lymphoepithelial lesions on FNAC smears, n=36

Category	Number	Percentage
1) Lymphoepithelial cyst	5	13.88
2) Lymphoepithelial sialadenitis (LESA)	16	44.44
3) LESA with a differential diagnosis of chronic sclerosing sialadenitis	7	19.44
4) LESA with a differential diagnosis of low-grade lymphoma	2	5.5
5) LESA with a differential diagnosis of Warthin's tumor	4	10.11
6) Suggestive of lymphoepithelial carcinoma	2	5.5

FNAC: Fine needle aspiration cytology

FNAC of these lesions predominantly showed numerous cyst macrophages admixed with benign reactive lymphoid cells.

Clinical presentation

Clinically, they present as slow-growing painless enlargement of the parotid gland with unilateral involvement of the gland in majority of the cases.

Clinical significance

Most of the lesions show complete cure by excision with no recurrence.

LESA

It constitutes part of a heterogeneous group of lesions of the salivary gland which have a prominent lymphoid component.

LESA is also known as Sjögren type sialadenitis.[14] The entity was first described by Johann von Mikulicz Radecki. In LESA, there is a benign lymphocytic infiltrate of the salivary gland with parenchymal atrophy and foci of ductal hyperplasia.[11]

Clinical presentation

Maybe seen isolated without any autoimmune disease associated with it or associated with Sjögren syndrome[11] or seen in HIV-positive individuals.[15]

It usually occurs in women and affects the parotid gland in 90% of cases.[14]

LESA in isolated cases (without Sjögren's syndrome)

May be unilateral (mostly) or bilateral slow-growing painless parotid enlargement.

LESA in Sjögren's syndrome

The typical clinical presentation is that of bilateral painless parotid enlargement along with the history of dry eyes and dry mouth with serological evidence of autoantibodies.

LESA in HIV-positive cases

Salivary gland disease in HIV patients is characterized by lymphoid hyperplasia in the parotid and sometimes in submandibular glands leading to the formation of two pathological entities, i.e., lymphoepithelial cysts and LESA. These lesions are also known as HIV-associated salivary gland disease (HSGD) or salivary diffuse infiltrative lymphocytosis syndrome.[15,16]

LESA in HIV patients is usually bilateral and accompanied by cervical lymphadenopathy.

On FNAC features diagnostic of LESA are the following (Figure 1)

- Cellular smears containing salivary gland ductal epithelial cells
- Numerous reactive lymphoid cells
- Exuberant ductal basal cell proliferation
- In our cases, most of the cases diagnosed as LESA by FNAC showed the features of numerous reactive lymphoid cells admixed with proliferating salivary gland ductal lining cells.

In the cases where squamous metaplastic components were seen, a D/D of chronic sclerosing sialadenitis was given (Figure 2) and in the cases where oncocytic cells were seen, a D/D of Warthin's tumor was given (Figure 3). In the cases in which predominantly the lymphoid component was sampled during FNAC, the D/D of low-grade lymphoma was given.

Clinical significance

LESA has indolent behavior. However, continuous follow-up is mandatory because of the increased risk of lymphoma development (marginal zone lymphoma).[17]

LEC

LEC is rare accounting for 0.4% of all malignant tumors of the salivary gland.[18-20] It is poorly differentiated neoplasms of epithelial cells resembling nasopharyngeal carcinoma.

Clinical presentation

It presents as painless enlargement of the parotid gland, with median age of diagnosis is 40 years, and has a female preponderance (F: M-3: 2).[20]

FNAC shows

- Highly cellular smears, large, pleomorphic cells, and lymphoid cells in the background
- Cytological smears with moderate cellularity have a close (D/D) of LESA.

Clinical significance

It is very much important to differentiate primary LEC from metastatic nasopharyngeal carcinoma (to the salivary gland) because of different modalities of treatment and prognosis.

Proper clinical examination and correlation with the radiological findings are needed to narrow down the (D/D).

Limitation of the study

1. Due to rarity of the LELs of the salivary glands in comparison to epithelial tumors, the sample size is small
2. Correlation with the radiological findings was not included due to their unavailability in some cases.

Future perspective

1. Using an objective digital image analysis, intraepithelial lymphocyte can be detected within the salivary glands[21] for faster and earlier diagnosis of the LELs
2. In lymphoid cell-rich lesions of the salivary gland, flow cytometric analysis[13] of the salivary gland aspirates obtained by FNAC might be used routinely to diagnose or exclude low-grade lymphoma of the salivary glands at the earliest.

CONCLUSION

LELs of the salivary gland are not only uncommon but also sometimes pose a great diagnostic dilemma for a definitive diagnosis.

They have a wide range of clinical presentations – in terms of consistency of the swelling, number of gland involved, association with autoimmune conditions, or HIV infection. In our study, we have highlighted the role of FNAC for the diagnosis of LELs of salivary gland and the diagnostic difficulties associated with it. Careful attention to the clinical history, clinical examination findings, adequate sampling, and good-quality smears play pivotal role for a definitive diagnosis of these lesions preoperatively.

PATIENT CONSENT FORM

In all the cases, consent was taken before performing the FNAC procedure.

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Authors' Contributions:
RP-Definition of intellectual content, literature survey, prepared the first draft of manuscript, implementation of the study protocol, data collection, data analysis; **SC**- Manuscript preparation, submission of article and Corresponding Author; **SM**-Concept, design, clinical protocol, manuscript preparation, editing, and manuscript revision; **CG**- Design of study, statistical analysis and interpretation, review manuscript

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