

Parotid lymphoepithelial cysts in human immunodeficiency virus: a review

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Abstract

Background: Many patients with human immunodeficiency virus present with atypical features. Early indicators of human immunodeficiency virus are scarce and hence most affected patients are diagnosed in the later stages of the disease, which is associated with poor prognosis. Salivary gland disease usually develops before acquired immunodeficiency syndrome, and is sometimes the first manifestation of human immunodeficiency virus infection. Salivary gland lesions include benign lymphoepithelial cysts of the parotid gland, which are seen in 3–6 per cent of patients. Many of the reported lesions are diagnosed on routine examination.

Objective: This review aimed to highlight the association between parotid gland benign lymphoepithelial cyst and human immunodeficiency virus infection, in order to aid early diagnosis and management of the disease.

Conclusion: Human immunodeficiency virus testing is recommended for patients with benign lymphoepithelial cysts, as this can often be the first indication of human immunodeficiency virus infection. Benign lymphoepithelial cysts are important diagnostic and prognostic indicators in human immunodeficiency virus infection.

Key words: Parotid Gland; Cyst; HIV; Diagnosis

Introduction

Benign lymphoepithelial cyst of the parotid gland is the most common salivary gland pathology in human immunodeficiency virus (HIV) patients.¹ The cysts are early indicators of HIV infection, with an incidence rate of 3–6 per cent in affected adults² and 30 per cent in the paediatric population.³

Hildebrandt (1895) was the first to report benign lymphoepithelial cyst of the parotid gland. Its association with HIV infection was first described by Ryan and colleagues in 1985.⁴

Lymphoid hyperplasia of the salivary gland is an important diagnostic and prognostic indicator in HIV infection, which may reflect a localised manifestation of persistent, generalised lymphadenopathy.⁴

Other parotid gland pathologies seen in HIV infection include: sicca syndrome, diffuse infiltrative lymphocytosis syndrome, parotitis secondary to infection, intraparotid lymphadenopathy, cryptococcus infection, benign lymphoepithelial lesions, and salivary gland neoplasms such as adenoid cystic carcinoma, Kaposi sarcoma and lymphoma.⁴

Aetiopathogenesis

Human immunodeficiency virus infection is associated with hyperplasia of the intraparotid lymph nodes with

interstitial lymphoid infiltrate. Parotid benign lymphoepithelial cysts occur secondary to this hyperplasia.²

There are two main hypotheses concerning the development of benign lymphoepithelial cyst. The ‘obstructive theory’ states that lymphoid proliferation in the parotid gland leads to ductal obstruction and salivary dilatation that mimics a true cyst.⁵ The other hypothesis states that HIV-related reactive lymphoid proliferation occurs in the lymph nodes of the parotid gland; the parotid glandular epithelium becomes trapped in normal intraparotid lymph nodes, resulting in cystic enlargement (Figure 1).⁵

Clinical features

Benign lymphoepithelial cyst affects males and females equally, and occurs in both adults and children.^{3,11} The cysts are painless, slow-growing,¹¹ frequently bilateral,^{4,11} soft in consistency and involve the superficial lobe of the parotid gland,⁴ with multiple cysts being more common than single.¹² Their size varies from 0.5 cm to 5 cm in diameter. Cervical lymphadenopathy¹² is evident in 50 per cent of patients.^{2,4} Parotid benign lymphoepithelial cyst rarely involves the facial nerve, and can cause gross facial deformities.

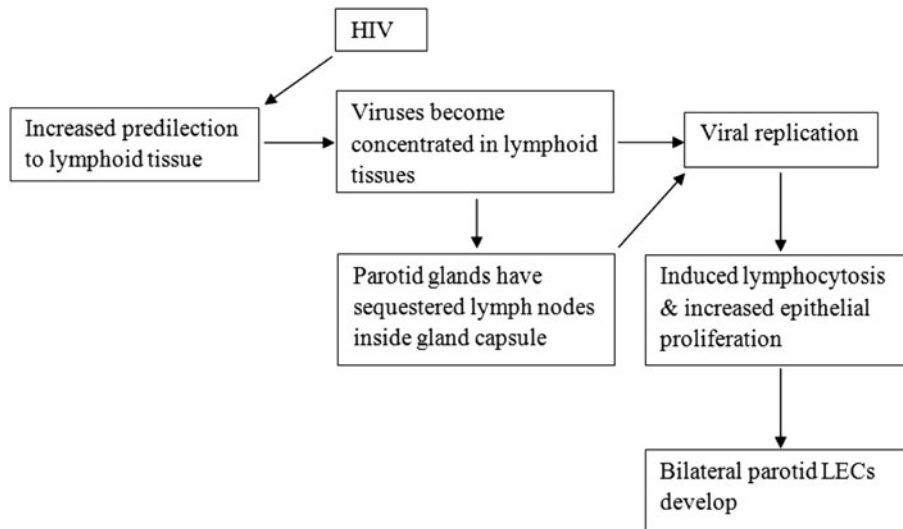


FIG. 1

Schematic representation of aetiopathogenesis of benign lymphoepithelial cyst in human immunodeficiency virus.⁶⁻¹⁰ HIV = human immunodeficiency virus; LEC = lymphoepithelial cyst

Non-HIV patients presenting with benign lymphoepithelial cyst can be differentiated from HIV-infected counterparts (Table I).

Numerous benign lymphoepithelial cysts are associated with a condition called diffuse infiltrative lymphocytosis syndrome, which is considered to be a subset of HIV that affects 1 to 2 per cent of patients.¹⁵ Prior to the

association between diffuse infiltrative lymphocytosis syndrome and HIV, diffuse infiltrative lymphocytosis syndrome was thought to be associated with Sjögren’s syndrome (Table II).^{7,15}

Investigations

Those diagnosed with parotid benign lymphoepithelial cysts, with or without systemic manifestations, should undergo tests for HIV infection. Other investigations might include fine needle aspiration cytology, imaging (e.g. ultrasonography, computed tomography (CT) and magnetic resonance imaging (MRI)), histopathology, immunoperoxidase studies and immunohistochemistry.

Fine needle aspiration cytology is considered to be the basic diagnostic tool for differentiating lymphoproliferative lesions (Table III).^{2,5,6,16}

Imaging modalities

Ultrasonography. Benign lymphoepithelial lesions in the parotid gland can manifest in HIV-positive patients with a wide spectrum of heterogeneous appearances

TABLE I BENIGN LYMPHOEPITHELIAL CYST IN HIV AND NON-HIV PATIENTS ^{2,3,13,14}		
Features	HIV cases	Non-HIV cases
Aetiopathogenesis	Mainly due to virus-induced lymphoid hyperplasia ²	Epithelial retention in oropharyngeal lymphoid organs ¹³
Clinical presentation	Bilateral presentation, most commonly located in parotid gland ^{2,13}	Unilateral presentation, most commonly located in cervical region ¹⁴
CT & MRI	Multicystic appearance ¹³ associated with cervical lymphadenopathy in all patients ³	Commonly unicystic ¹⁴
Malignant transformation	May or may not undergo malignant transformation (mainly lymphomas) ¹³	Usually no malignant transformation
Bcl protein expression	Absence of Bcl-2 protein expression ²	Strongly Bcl positive ²
Recurrences	Present ¹³	Absent ^{13,14}
Prognosis	Poor ¹³	Better ¹³
HIV = human immunodeficiency virus; CT = computed tomography; MRI = magnetic resonance imaging; Bcl = B-cell lymphoma		

TABLE II DIFFUSE INFILTRATIVE LYMPHOCYTOSIS SYNDROME AND SJÖGREN’S SYNDROME COMPARISON ^{6,15}	
Diffuse infiltrative lymphocytosis syndrome	Sjögren’s syndrome
Increased enlargement of parotid gland	Less enlargement comparatively
Increased extra-glandular involvement	Less extra-glandular involvement
Antigenically-driven response	Mainly autoimmune
Paucity of antibodies	Increased antibodies
Cystic involvement in lymph nodes entrapped in gland, or in nodes outside gland but within capsules	Involvement of parenchyma in salivary gland

TABLE III
FNAC FINDINGS IN VARIOUS LYMPHOPROLIFERATIVE LESIONS^{2,5,6,16}

Lymphoproliferative lesion	FNAC findings
Benign lymphoepithelial cyst	Characteristic triad of squamous cells, lymphocytes & foamy macrophages
Warthin's tumour	Brown, mucoid fluid with oncocytic cells in cohesive monolayered sheets
Hodgkin's lymphoma	Typical Reed–Sternberg cells or atypical mononuclear Hodgkin cells with lymphocytes, eosinophils, plasma cells & histiocytes
Non-Hodgkin's lymphoma	Monotonous population of large, atypical lymphoid cells with non-cleaved, multiple nucleoli & scanty basophilic cytoplasm

FNAC = fine needle aspiration cytology

sonographically, ranging from simple cysts to mixed masses.¹⁷

Benign lymphoepithelial cysts typically appear as prominent round hypoechoic areas, ranging from 0.5 cm to 5 cm in diameter, with well circumscribed margins, internal septations and posterior acoustic enhancement.³

Computed tomography and magnetic resonance imaging. Multiple small cysts with enlarged parotid glands are usually observable on CT and MRI scans. Computed tomography can demonstrate cervical lymphadenopathy in 100 per cent of cases.⁷ However, these features are non-specific and are not diagnostic of benign lymphoepithelial cyst, and hence are used only as diagnostic adjuncts for surgery.¹¹

TABLE IV
CONDITIONS MIMICKING BENIGN LYMPHOEPITHELIAL CYST^{6,12,15,16,19}

Condition	Features
Reactive lymphadenopathy Sjögren's syndrome	Firm, nodular, submucosal, tender masses; rare in parotid regions ⁶ Bilateral diffuse enlargement of both glands; characteristic multicentric, cystic appearance; less extra-glandular manifestation; cysts occur in parenchyma ¹⁵
Warthin's tumour	Unilateral; predominantly affects males & older individuals; painless, firm, circumscribed cystic masses; no cervical lymphadenopathy; bilayered cuboidal, columnar or oncocytic ductal epithelium ¹⁹
Extra-nodal malignant lymphoma	Lymphadenopathy elsewhere in body; involvement of facial nerve; may present as rapidly growing masses in gingiva, palate with bone destruction, tongue, or tonsillar fauces ¹⁶
Lymphocytic sialadenitis	Bilateral disease; recurring, progressive swelling with discomfort or pain ¹²

Histopathology

Histopathology of benign lymphoepithelial cyst reveals a cystic wall formed of multi-layered squamous epithelium comprising germinal centres and dense lymphoid infiltrate. Pale homogeneous material with foamy macrophages and lymphocytes are seen in the lumen. The salivary glandular parenchyma adjacent to these cysts appears normal.^{7,15}

Immunoperoxidase studies

Positivity for cytokeratin reveals the epithelial origin of benign lymphoepithelial cyst. Positive staining for cluster of differentiation antigens 45, 20, 79a and 3 indicates a lymphoid component to the cysts.¹⁸

Immunohistochemistry

Immunohistochemistry highlights the reactive nature of benign lymphoepithelial cysts.² Active replication is indicated by the presence of HIV proteins or RNA on the cells of the salivary gland lymphoid follicles (Table IV).⁶

Management

Treatment for benign lymphoepithelial cyst is sought mainly for cosmetic reasons, as most patients are asymptomatic. Fine needle aspiration cytology or biopsy with adjunctive imaging can indicate malignant transformation, which has to be managed accordingly.⁴

The combination of azathioprine with newer protease inhibitors is successful in treating benign lymphoepithelial cyst, especially when it coincides with diffuse infiltrative lymphocytosis syndrome. This treatment, which may be used in combination with corticosteroids, seems to be the most effective means of treating the parotid swellings of patients with diffuse infiltrative lymphocytosis syndrome. Patients who do not qualify for anti-retroviral therapy can undergo alcohol sclerotherapy, which is considered to be an effective, safe and simple treatment of diffuse infiltrative lymphocytosis syndrome. Doxycycline sclerotherapy has been used in younger patients to avoid surgery.⁴ Superficial parotidectomy is favoured over enucleation in the treatment of benign lymphoepithelial cyst owing to the latter's high recurrence rate.⁴

Conclusion

Benign lymphoepithelial cyst can be an early indicator of HIV infection. The cysts are also rarely seen in non-HIV positive patients; HIV testing is mandatory for all patients presenting with these cysts. It is imperative that oral physicians are aware of this entity, which may mimic other parotid pathologies owing to its atypical features.

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Dr K Babitha takes responsibility for the integrity of the content of the paper

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