

Lymphoepithelial lesions of the parotid gland in the HIV era – a South African experience

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Summary

Objective. Historically, lymphoepithelial lesions (LELs) have been a peripheral indication for surgery on the parotid gland, accounting for less than 1% of all parotidectomies undertaken. In the HIV era the profile of parotidectomy has changed, with LEL becoming a common indication for parotidectomy, prompting a review of our current experience.

Design. A retrospective study was undertaken between January 1998 and December 2005.

Setting. Surgical services at King Edward VIII Hospital, Durban.

Subjects. All patients presenting with parotidomegaly.

Results. One hundred and sixty-two patients with parotidomegaly were evaluated; 53 (32.7%) had LEL lesions. A total of 151 parotidectomies (including 42 parotidectomies undertaken for LEL lesions) were performed in 147 patients. Radiotherapy was offered to 11 patients with LEL lesions. Complications following parotidectomy for LEL included facial nerve palsy ($N = 3$), seroma formation ($N = 5$) and facial artery false aneurysm ($N = 1$). Three patients required re-parotidectomy for recurrent LEL parotidomegaly. In the patients who underwent radiotherapy, there was a satisfactory outcome; 2 patients who received 4 Gy radiation per sitting developed mild skin discolouration of the treated area.

Conclusion. Although surgical management of LEL parotidomegaly may provide a satisfactory result, this approach is technically challenging and is associated with complications and recurrences. For these reasons, the non-operative approach employing radiotherapy should be considered.

The parotid gland is host to a spectrum of pathology including inflammatory (and infective) conditions, and neoplastic enlargement. In most surgical practices, parotidectomy has

traditionally been undertaken for benign (largely pleomorphic adenomas) and malignant conditions. Historically, lymphoepithelial lesions (LELs) have been a peripheral indication for surgical intervention on the parotid gland, accounting for less than 1% of parotidectomies undertaken in most series.^{1,2} LEL has been variably designated as Sjogren-like syndrome, benign lymphoepithelial lesion, cystic lymphoepithelial lesion, HIV salivary gland disease and lymphoepithelial cyst. Increasingly, in our practice, the profile of parotidectomy has changed, with LEL becoming a common indication for parotidectomy, prompting a review of our current experience.³

Patients and methods

A retrospective study was undertaken of patients who presented with parotidomegaly to the surgical services at King Edward VIII Hospital, Durban, to evaluate the impact of LEL of the parotid gland on our surgical practice. The study was conducted over an 8-year period between January 1998 and December 2005.

The demographic profile of the patients, their clinical presentation, the pathology encountered, the extent of the parotidectomy, postoperative complications and response to radiotherapy were documented.

In addition to standard haematological and biochemical testing, the pre-operative evaluation included routine chest radiography and fine-needle aspiration biopsy (FNAB); computed tomography (CT) scan was selectively performed in cases of diagnostic ambiguity. In the appropriate clinical scenario (when LELs were suspected or confirmed histologically), the HIV status of the patient was evaluated.

Between 2003 and 2005 increasing awareness of LEL and the complications associated with its surgical treatment prompted the use of radiotherapy; a total of 24 Gy was administered in equal divided doses over 12 days.

Patients were reviewed at 1 week, 3 months and then selectively following treatment. Compliance with follow-up in our practice, which largely serves a working-class population, is notoriously poor; however we have an effective self-referral service.

Results

One hundred and sixty-two patients with parotidomegaly were evaluated during the study period; 53 patients had LEL lesions. A total of 151 parotidectomies (including 42 parotidectomies undertaken for LEL lesions) were performed in 147 patients; parotidectomy was undertaken bilaterally in 4 patients. Radiotherapy was offered to 11 patients with LEL lesions.

LEL accounted for 53 (32.7%) of all cases of parotidomegaly evaluated (versus 54 patients (33%) with pleomorphic adenoma). Females ($N = 39$) were more commonly affected than males ($N = 14$). The mean age at presentation was 26 years (range 2 - 47 years), and 7 patients were less than 6 years old.

Until 2003, LELs were the commonest indication for undertaking parotidectomy, accounting for 34.3% of all parotidectomies undertaken between 1998 and 2003. The indications for parotidectomy are outlined in Table I. All patients with LEL presented with painless, non-fluctuant parotidomegaly that was cosmetically unacceptable to them. This was noted to be bilateral in 39 of the 53 patients treated; invariably the parotidomegaly was more pronounced on one side.

TABLE I. INDICATIONS FOR PAROTIDECTOMY (1998 - 2005)

Indications	<i>N</i>
Lymphoepithelial lesions	42*
Pleomorphic adenoma	54
Malignancy	42
Monomorphic adenoma	6
Chronic inflammation	4
Simple cyst	3
Total	151

* Between 2003 and 2005, a further 11 patients with LEL were treated with radiotherapy.

In all patients with LEL the parotidomegaly had been present for at least 6 months. The parotidomegaly was typically pronounced along the tail of the gland (Fig. 1). All patients were noted to be in satisfactory general condition, and the systemic examination was consistently normal.

Investigations

The haematological results for patients with LEL were within the normal range. The mean haemoglobin level was 12.9 g/dl (range 11.2 - 15.9 g/dl) and the mean white cell count was $9.4 \times 10^9/l$ ($5.1 - 11.4 \times 10^9/l$). The mean serum albumin level was 29.2 g/dl (range 29 - 34 g/dl).

In all patients with LEL, FNAB consistently excluded the possibility of malignancy, demonstrating mainly lymphocytes and a few polymorphs with occasional epithelial cells. FNAB provided a pre-operative diagnosis of LEL in 23 patients.

HIV status was known to be positive in 19 patients preoperatively; these patients were not on antiviral therapy. Twenty-seven patients were confirmed HIV-positive on serological testing undertaken post-parotidectomy, and all HIV-positive patients were referred for antiviral therapy.

Seven patients declined HIV testing.

Imaging of the parotidomegaly was undertaken during the early period of the study; ultrasonography confirmed the cystic nature of the condition in all 30 patients who had this variant of LEL lesion. CT scan was utilised selectively (in 24 patients) and typically demonstrated the cystic lesions as well-circumscribed low-density areas (Fig. 2).



Fig. 1. Clinical photograph demonstrating lymphoepithelial parotidomegaly. Note the typical enlargement along the tail of the parotid gland.

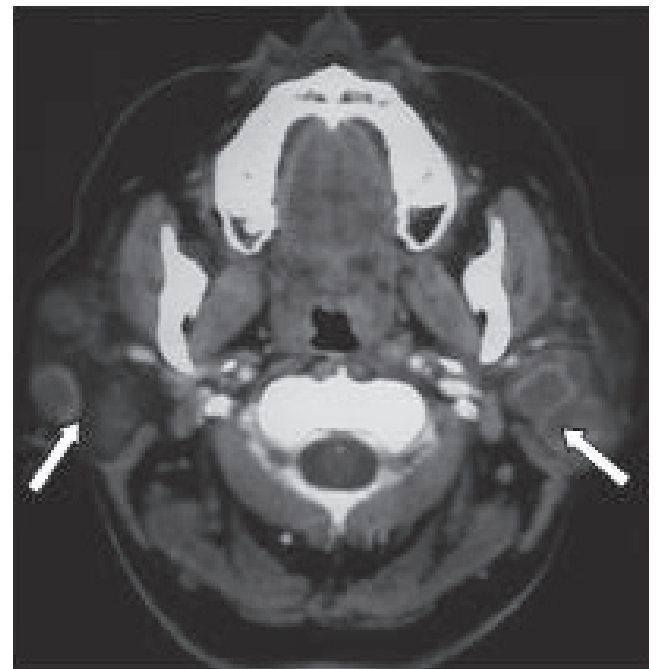


Fig. 2. Computed tomography scan demonstrating bilateral lymphoepithelial cystic lesions of the parotid gland (indicated by arrows).

Surgery

Superficial parotidectomy was undertaken during the early period of the study (during 1998 and 2003) because of diagnostic uncertainty and for cosmesis. With the increasing clinical appreciation of LEL lesions, parotidectomy for this condition was undertaken mainly for cosmesis.

Complications following parotidectomy for LEL included facial nerve palsy ($N = 3$), seroma formation ($N = 5$) and facial artery false aneurysm ($N = 1$).

All patients presented for review 1 month after surgery and thereafter at 3-monthly intervals, selectively; 4 patients were lost to review at 3 months. In 2 patients the facial nerve palsy

resolved spontaneously within 6 months of surgery.

Three patients (one at 8 months, the second at 18 months and the third at 20 months) required re-parotidectomy for recurrent LEL parotidomegaly.

All but 2 patients (1 who required the ligation of a facial artery false aneurysm and the other with persistent facial nerve palsy) were satisfied with the eventual outcome of surgery.

Radiotherapy

During the latter period of the study (between 2004 and 2005) the clinical awareness of LELs and the complications that followed parotidectomy for this condition prompted the use of radiotherapy as a therapeutic option in 11 patients. Three patients did not avail themselves of this therapy and were subsequently lost to follow-up. In the 8 patients who underwent radiotherapy, there was a satisfactory outcome when these patients were reviewed at 3 months. Two patients who, for logistical reasons, were subjected to 4 Gy radiation per sitting developed mild skin discolouration of the treated area; notwithstanding this, they deemed the outcome satisfactory.

Pathology

Histopathological appraisal of the LEL confirmed lymphoepithelial cysts (LECs) in 30 cases and myoepithelial sialadenitis (MESA) in 13 cases.

LEC was characterised by multiple parenchymal cysts of varying size and shape. The cysts were lined with either multiple layers of flattened epithelial or stratified squamous epithelial linings. The epithelium was intimately associated with reactive lymphoid follicles containing germinal centres of varying size and shape. Folliculolysis was variably present. Single and aggregates of lymphocytes were noted in the cyst epithelium. Also noted were scattered giant and plasma cells.

MESA was characterised by single and aggregates of lymphocytes within the glandular epithelium and a dense infiltrate of lymphocytes and plasma cells with the formation of epimyoeplithelial islands. The plasma cells were polyclonal. Confluent proliferation of monocytoid B cells was not evident. No case of high-grade lymphoma was noted.

Discussion

Salivary gland enlargement is a relatively uncommon problem, accounting for approximately 3% of all head and neck tumours, with the parotid gland accounting for about 70% of these lesions.^{4,5} Of these, between 70% and 80% are benign and between 60% and 90% are pleomorphic adenomas.^{1,6-8} In this review a steady decline in the incidence of pleomorphic adenomas and the emergence of LEL as the major cause of benign parotid gland enlargement was noted. Early in our experience LELs were not widely recognised as a manifestation of HIV disease. In current practice, regardless of the patient's HIV status, the presentation of bilateral, painless and multicystic parotidomegaly heralds the diagnosis of LEL, to the extent that ultrasonography and CT have now become unnecessary diagnostic tools. However, fine-needle aspiration cytology is recommended to exclude the possibility of other lesions such as lymphoma or Kaposi's sarcoma.

Failure to recognise this condition leads to belated diagnosis and delayed treatment.

Lymphoid proliferations of the salivary gland may be reactive or neoplastic. Simple LECs occur sporadically, typically in middle-aged men, unrelated to HIV disease. They are unilocu-

lar non-recurrent cysts lined with squamous, columnar, respiratory or mixed epithelial types.⁹

LELs are most commonly associated with HIV infection or AIDS but have also been described in normal or other immunocompromised patients, implying a direct role for HIV, Epstein-Barr Virus (EBV) and ductal obstruction caused by florid lymphoid hyperplasia. LEL cysts are multiple or single and uni- or multilocular in nature. The epithelium of larger cysts may be infiltrated by lymphocytes, mostly CD20+ B-lymphocytes, while the epithelium of smaller cysts contains mainly CD3+/CD4+ T-lymphocytes. In addition, aggregates of lymphoid cells in a nest are variably present.¹⁰

Mikulicz is credited with the first description of salivary gland LEL in 1885, followed in 1895 by Hilderbrandt's report.^{2,11} In 1985 Ryan *et al.*¹² were the first to identify this condition in HIV-positive patients. In a review by Ethunandan *et al.*¹ LEL lesions accounted for less than 1% of all parotidectomies performed over a 26-year period (1974 - 1999); in contrast, in this study, LEL accounted for 32% of all parotidectomies undertaken.

The emergence of the HIV pandemic has been associated with a steady increase in the frequency of parotid LEL lesions so that the latter emerges as the commonest cause of parotidomegaly in most surgical practices.^{2,3,13,14} Furthermore, these lesions have become a well-described marker for HIV infection, occurring in about 5% of HIV-positive patients; indeed the presentation of this lesion may be the first sign of an otherwise unappreciated HIV infection.¹⁵⁻¹⁷ Some centres are even recognising it as a marker for AIDS.

The exact aetiology of these lesions is unknown and remains speculative. Bernier and Bhaskar¹⁸ have defined benign lymphoepithelial cysts as solitary or multiple cysts within lymph nodes, trapped during the parotid gland embryogenesis; these represent cystic degeneration of salivary gland inclusions within these intra-parotid lymph nodes. These intra-parotid gland lymph nodes are largely located along the tail of the gland, thereby predisposing this part of the gland to early enlargement. HIV has a predilection for lymphoid tissue and high concentrations of the virus can be found within these nodes. With progressive cystic degeneration there is eventually spread of the inflammatory process to the entire lobe.¹⁹

The currently available management options for LEL include: (i) simple aspiration; (ii) antiretroviral therapy; (iii) radiotherapy; and (iv) surgery – either enucleation of cysts or parotidectomy.

Aspiration provides a temporary reprieve as cysts eventually recur; the use of intra-lesional tetracycline injections to induce sclerosis has proved to be less than satisfactory. Furthermore, cysts are of varying size, multiple and loculated, thereby making complete aspiration difficult.^{20,21}

When the HIV status is known, antiretroviral therapy has been shown to be promising in the management of LEL, in combination with a short course of tapered-dose steroids. These agents have been reported to produce dramatic reduction in parotidomegaly.^{14,22,23} The durability and effectiveness of antiviral therapy compared with other forms of treatment is presently unknown. Furthermore, availability and compliance with antiviral therapy may be problematic.

Impressive results have been reported with the early use of external-beam radiation therapy. Early studies²⁴ reported that doses of 8 - 10 Gy produced satisfactory early clinical responses. However the early results were not shown to be durable, with most lesions recurring within a year; furthermore,

re-treatment for treatment failures and recurrent disease after the use of 8 - 10 Gy has been unsatisfactory. Beitler *et al.*²⁵ have produced more satisfactory results with a 24 Gy dose, in daily 1.5 Gy fractions. The cosmetic results have been reported to be durable for 24 months. Recurrences after 24 months were uncommon and the side-effects tolerable.²⁵ However, radiotherapy may be a scarce and pressurised resource, particularly in centres (such as ours) that are in the midst of the AIDS pandemic. In this study the outcome following radiotherapy was excellent, the only side-effects being facial discolouration at the site of radiotherapy in 2 patients who received 4 Gy fractions (for service logistical reasons) as opposed to the protocol of administering 24 Gy in divided doses of 2 Gy per session.

Historically, operative intervention has been the management of choice. In the light of surgical complications associated with surgery and the recognition that radiotherapy is effective therapy, there has been a gradual shift towards non-operative intervention for a condition that is essentially benign.

While our experience has shown that surgical therapy may be a viable option offering durable results with satisfactory cosmesis, operative intervention for LEL (as opposed to other benign conditions) is technically challenging. Surgery may indeed be the only option in those centres where radiotherapy is not readily available.

The underlying sialadenitis and cystic changes associated with LEL displace the facial nerve so that the standard landmarks pivotal for safe and effective parotidectomy may not be readily defined. Injury to the facial nerve, bleeding and seroma formation are therefore not uncommon complications. Furthermore, involvement of the superficial and deep lobes suggests that the only effective procedure would be a total parotidectomy; the 3 patients with recurrent disease in this series had previously undergone superficial parotidectomy.

The optimal management of LEL remains controversial in the absence of comparative studies; to date, the management options for LEL have been based on case reports and retrospective studies that invariably reflect institutional bias prompted by the availability of resources (the ready access to antiretroviral therapy, radiotherapy and technical competence).

In the light of our experience and the current literature a management algorithm is proposed (Fig. 3).

Conclusion

In the HIV era LELs are becoming an increasingly common cause of parotid gland enlargement. This study has demonstrated that while surgical management may provide a satisfactory result, this approach is technically challenging, and is associated with complications and recurrences. For these reasons, the non-operative approach employing radiotherapy should be strongly considered.

The authors thank the Ethics Committee, Nelson R Mandela School of Medicine, and the management of King Edward VIII Hospital for their support in undertaking this study.

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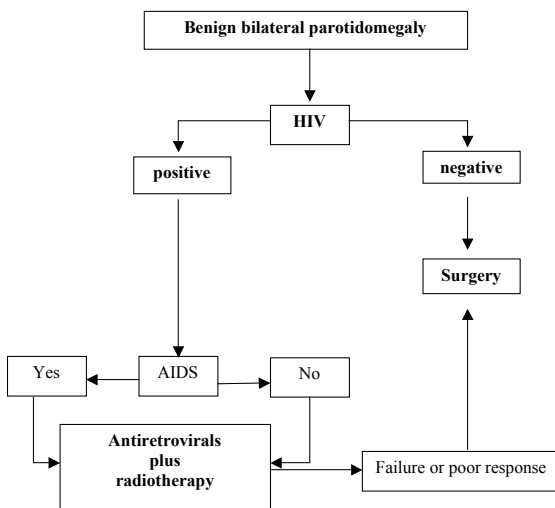


Fig. 3. Algorithmic approach to the management of lymphoepithelial parotidomegaly.