Familial Clustering of Parotid Gland Lymphoepithelioma in North America

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ABSTRACT
Objective: To describe genetic susceptibility in the first familial clustering of parotid gland lymphoepithelioma reported in North America.
Design: Retrospective study.
Setting: Tertiary care institution with outreach to northern Quebec.
Methods: Chart, family history, literature review, and c-kit assay.
Main Outcome Measure: C-kit assay.
Results: Four family members of both sexes over two generations had lymphoepithelioma of the parotid gland, without involvement of the nasopharynx. Two c-kit assays were positive of the three cases that could be done. Association with Epstein-Barr virus has been demonstrated in the oncogenesis of lymphoepithelioma.
Conclusion: Genetic susceptibility and common familial environmental factors play a role in the development of parotid gland lymphoepithelioma. A complete family history should be obtained in all cases of lymphoepithelioma of the parotid gland.

SOMMAIRE
Objectif: Décrire la susceptibilité génétique dans le premier regroupement familial signalé en Amérique du Nord sur le lymphoépithéliome de la glande parotide.
Devis: Étude rétrospective.
Localisation: Établissement de soins tertiaires avec point de service dans le nord québécois.
Méthodes: Dossiers, antécédents familiaux, revue de la littérature, et c-kit.
Variable évaluée: C-kit.
Résultats: Quatre membres de la famille, des deux sexes, sur deux générations avaient un lymphoépithéliome de la glande parotide, sans implication du nasopharynx. Deux dosages avec le c-kit ont été positifs sur les trois cas qui pouvaient être évalués. L’association avec EBV a été démontrée dans l’ontogenèse des lymphoépithéliomes.
Conclusion: La susceptibilité génétique ainsi que des facteurs environnementaux communs familiaux jouent un rôle dans le développement des lymphoépithéliomes de la glande parotide. Une histoire de famille devrait être obtenue dans tous les cas de lymphoépithéliome de la glande parotide.

Key words: genetics, lymphoepithelioma, parotid cancer

Lymphoepithelioma is a rare, nonkeratinizing, undifferentiated squamous cell carcinoma marked by a significant reactive lymphocytic infiltrate. It usually arises in the nasopharynx and less frequently in the salivary glands. We report on the first documented case in North America of several members of the same family affected by this rare salivary gland tumour. This is also the first report of this tumour affecting both sexes within the same family.
Case Reports

Case 1

A 27-year-old Inuit man was referred to the otolaryngology clinic for evaluation of a slowly growing left neck mass first noticed 7 months earlier. The patient reported a 2-month history of a burning sensation and numbness in the mandibular branch of the trigeminal nerve. Physical examination revealed a 4 cm mass inferior to the ear, extending from the mastoid to the angle of the mandible. This was confirmed with magnetic resonance imaging (MRI): T1-weighted MRI emphasized a 32 × 31 × 37 mm mass involving the superficial and deep lobes of the left parotid gland, extending into the floor of the auditory canal. Concurrent findings were an enlarged jugulodigastric node, 16 × 11 mm. Two fine-needle aspiration cytology (FNAC) specimens were inconclusive. Panendoscopy ruled out any unknown primary tumours, such as nasopharyngeal cancer. The third FNAC and an open biopsy of a cervical node were consistent with large cell, undifferentiated carcinoma. Since it portended a potentially aggressive course, a decision was made to proceed with a total parotidectomy and neck dissection followed by external beam radiotherapy. Tumour removal included a radical parotidectomy and resection of the inferior and lateral temporal bone. This was followed with grafting of the facial nerve using a sural nerve graft. Facial nerve function outcome was a House-Brackmann grade 3. Pathologic examination of the parotid gland specimen and the associated cervical nodes (1 of 4) demonstrated lymphoepithelioma (LE). The patient is now 5 years post-treatment and is free of disease.

Case 2

A 34-year-old Inuit female and cousin of case 1 was referred to the otolaryngology clinic for evaluation of a right-sided cervical mass that had swollen noticeably in the last 2 weeks, accompanied by fever. The patient responded well to antibiotics, and the swelling regressed. However, the mass persisted: it appears that the mass had compressed the remaining normal parotid gland and led to parotitis. Computed tomography (CT) of the neck confirmed a parotid mass and demonstrated an intraparotid necrotic node (Figure 1). Panendoscopy was undertaken: inspection and biopsy of the nasopharynx demonstrated no cancer. FNAC of the parotid gland revealed LE. Investigation for concurrent gynecologic cancer was negative. The patient underwent complete parotidectomy and neck dissection, followed by radiotherapy. The facial nerve was preserved. The patient is now 2 years post-treatment and free of disease.

Case 3

A 73-year-old male, who is the maternal uncle of cases 1 and 2 (Figure 2), presented with a mass in his parotid gland. FNAC was inconclusive, so an open biopsy was

Figure 1. Computed tomographic scan of case 2. The arrow is pointing to the right-sided parotid tumour. Anterior and central to the parotid tumour is the enlarged neck node.
performed. The pathology resembled that of the two other patients. Owing to his overall health status, he was treated only with radiotherapy. He is now free of disease 2 years post-treatment.

Case 4

The aunt of the first two patients and sister of case 3 was diagnosed at age 57 years with the same pathology. She was likewise treated with complete parotidectomy and neck dissection, followed by radiotherapy to the neck and parotid gland. She initially did well but within a year developed seizures. CT of the brain revealed metastatic disease. She received palliative radiotherapy to the brain but eventually died 2 years after the diagnosis.

Discussion

Salivary gland tumours make up 1 to 2% of cancers in humans. Eighty percent arise within the parotid gland, and 15 to 30% of these are malignant. LE, also called undifferentiated carcinoma, is classified as World Health Organization type 3 nasopharyngeal carcinoma (NPC). The term lymphoepithelioma refers to its histopathologic characteristic of nonkeratinizing, undifferentiated squamous cell carcinoma with a reactive lymphocytic infiltrate (Figure 3). LE is found in the nasopharynx and salivary glands. Similar lesions in the stomach, skin, cervix, urinary bladder, thymus, lung, laryngopharynx, and oral cavity are classified as lymphoepithelioma-like carcinoma (LELC), the difference being the anatomic location. LE has been reported predominantly within the Inuit community of Greenland and in the Chinese. Familial clustering has only been reported in Greenland Eskimos. This case in northern Canada similarly affected a family but differs in that the patients represented both sexes.

In the management of parotid LE, it is very important to rule out a metastatic NPC that could present as a parotid mass by a thorough examination, imaging, or biopsy. Primary nasopharyngeal LE is sensitive to radiotherapy. Also, females should be screened with a gynecologic examination for concurrent LELC cervical tumours. Like other parotid malignancies, primary parotid LE treatment should include surgical excision of the parotid gland followed by radiation of the primary site. The clinical N0 neck should be addressed either by neck dissection or radiotherapy. Indeed, according to Stennert and colleagues, 45% of N0 salivary gland cancer has occult neck metastasis. The 5-year survival rate is 70 to 85%. Prognosis might correlate with the degree of lymphoid infiltrate, like other neoplasms. Lymphocytes destroy cancer cells, and it has been postulated that they prevent metastasis. In NPC, a marked lymphoid infiltrate is associated with rare cervical nodal metastasis and indicates a favourable prognosis.

LE of the parotid gland is strongly associated with Epstein-Barr virus (EBV), which also plays a role in Burkitt lymphoma and Hodgkin lymphoma. EBV infection seems to be an early step in LE of the parotid. Latent membrane protein 1 from EBV deregulates epithelial growth and differentiation of the primitive pharynx, leading to clonal expansion of these cells. LEs in non-Eskimo or Asian patients are usually EBV negative, as well as most LELCs. Since EBV is found in high prevalence in most populations, other genetic and environmental factors must contribute to the multistep disease progression in
high-risk populations. It has also been suggested that EBV might also play a role in the transformation of benign parotid gland lesion into malignant undifferentiated carcinoma ex pleomorphic adenoma.11

Genetic factors have not been studied for LE of the salivary gland, but considerable genomic research has been done for the nasopharynx. A genome-wide scan in Chinese familial clustering of NPC has shown evidence of many susceptibility loci for NPC: chromosome translocation t(1;3) and loss of heterogeneity on chromosomes 3p21-26, 4p15.1-q12, and 9p21-22.12,13 Chromosome 3p21 is associated with most human epithelial malignancies (small cell lung cancer, breast cancer, cervical cancer, renal cell adenoma, and head and neck cancers) because a tumour suppressor gene cluster resides on that locus.13

In our first two cases, c-kit assay was positive by immunochemistry, whereas it was negative in case 3. The proto-oncogene c-kit is a receptor tyrosine kinase that plays a role in the development of hematopoietic, melanocyte, and germ cell lines. It has been found in association with LE of the salivary glands. In LE, c-kit is overexpressed by a mechanism other than mutation.14 It is also involved in the development of breast cancer, acute myeloblastic leukemia, lung cancers, and other tumours. EBV and c-kit were implicated in a case of B-cell lymphoma of the brain developing in a patient with myelodysplastic syndrome.15 The possibility of using imatinib (also known as Gleevec, Novartis Pharmaceuticals, New Jersey, USA), which targets c-kit mutations, as a therapy for recurrences of LE or as an adjuvant postoperatively would be a future treatment to study.

Research looking into environmental contributors to LE has been inconclusive. No difference in lifestyle has been proven to contribute to LE of the salivary gland.3 A high content of nitrosamine in Chinese and Greenland food has been observed, and this agent is mutagenic in vitro.

With the sequencing of the human genome, the genetic component to this disease should soon be elucidated. It is hoped that the familial clustering of this disease will aid researchers in better understanding this cancer.

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References