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Lymphoepithelioma-like carcinoma of the parotid gland in a patient with rheumatoid arthritis

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ABSTRACT

Lymphoepithelioma-like carcinoma (LELC) is an Epstein-Barr virus (EBV) related malignancy. It is not a common condition and is usually found in the head and neck region. We describe the development of LELC involving the parotid gland in a patient with rheumatoid arthritis (RA) who had been receiving long-term azathioprine. A brief review is also made on the clinical presentation and histological features of LELC and the association of RA with EBV related diseases. The latter may be attributed to an increase in risk of malignancy associated with RA or as a result of the long-term immunosuppressive used.

Case report

A 52-year-old lady was diagnosed to have rheumatoid arthritis (RA) in 1987 when she presented with polyarthritis involving small finger joints, wrists and ankles. She denied dry eyes and dry mouth. Shirmer's test was negative. There was no evidence of extra-articular manifestations of the disease. Her rheumatoid factor was elevated (229 IU/ml, normal < 30 IU/ml). Her anti-extractable nuclear antigen antibody status was negative. She was given hydroxychloroquine 200 mg daily for more than 6 months with no clinical improvement and oral gold (auranofin 6 mg daily) was used instead. Her condition improved subsequently but her arthritis relapsed three years later. X-rays showed erosion of the carpal bones, radioulnar joints of hands, tarsal bones and metatarsal bones of both feet. Her therapy was switched to azathioprine 100mg daily in 1990 and she responded well.

In November 2000, she was incidentally found to have swelling of her right parotid gland. There were no other palpable lymph glands in the cervical, axillary and groin regions. Her complete blood count was normal and liver and renal function tests were unremarkable except for mildly elevated globulin level of 47 (normal 24-36) g/L. Erythrocyte sedimentation rate was 77 mm/hr and c-reactive protein was < 0.4 (normal < 1) mg/dl. Clinically there was no active synovitis to account for the elevated inflammatory markers. Trucut biopsy of the parotid mass showed syncytial sheets of cohesive epithelial tumour cells in a background of heavy lymphoplasmacytic infiltrate (Fig. 1). These epithelial tumour cells were cytologically malignant with prominent nucleoli, and their epithelial nature was confirmed by the strong immunoreactivity for cytokeratin (CAM5.2). *In situ* hybridization (ISH) study showed that the tumour cells were positive for Epstein-Barr virus-related RNA (EBER), further confirming the morphologic diagnosis

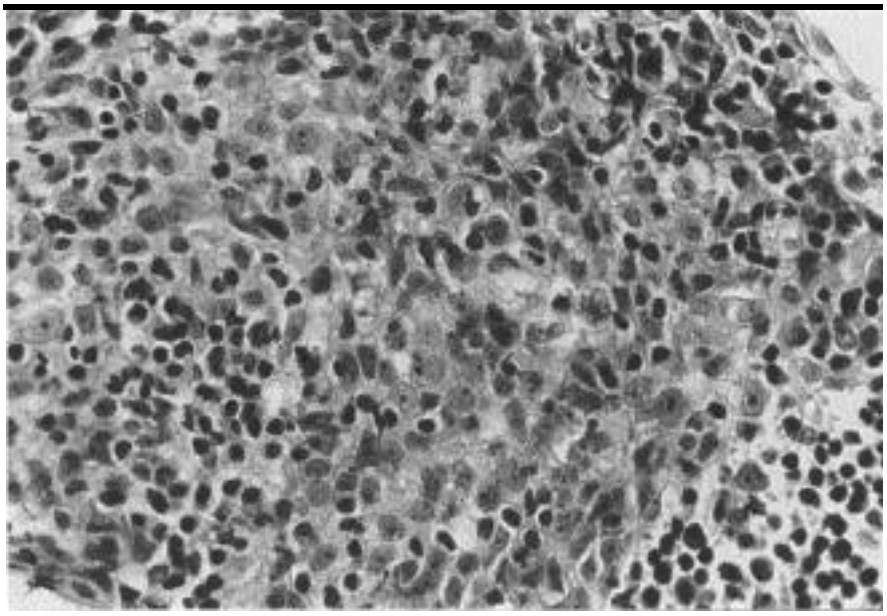

Fig. 1. Syncytial sheets of malignant cells against a heavy background of lymphoplasmacytic cells.

of a lymphoepithelioma-like carcinoma (LELC) (Fig. 2). She had taken a cumulative dose of 279.9 g of azathioprine at that time and she was asked to withhold the medication.

She was referred to the ENT surgeon for nasopharyngeal examination. The nasopharynx was smooth and blind biopsy showed normal histology. She was then referred to the radiologist for local radiotherapy. Her parotid mass subsided after radiotherapy but her condition was complicated by marked dry mouth and oral candidiasis. Nystatin suspension and Dispirin mouthwash were prescribed for symptomatic relief. There was no indication for disease modifying agents at this juncture, as the arthritis status had remained quiescent.

To summarise, we report here a lady suffering from seropositive RA treated with azathioprine for 10 years and developed LELC in her parotid gland. LELC classically occurs in the nasopharynx in the Orientals. Virtually 100% of LELC of the nasopharynx are Epstein-Barr virus-related. LELC can also occur elsewhere in the body, such as major salivary glands, thyroid gland, thymus, stomach, lung and a variety of other sites (1). Interestingly, those LELCs that occur in organs derived from the embryonic foregut are EBV-related (2). This strong association of such tumors with EBV has been found to be of diagnostic value for determination of the possible site of primary tumor in patients presenting with nodal metastatic disease.

Discussion

LELC of the major salivary gland is a rare disease, and affects mainly Orientals. The main histological differentiation of LELC is lymphoepithelial sialadenitis, a condition that not uncommonly affects the salivary glands in patients with autoimmune disease. In LELC, the epithelial tumor cells show malignant cytologic features. ISH study for EBER is extremely useful in that it is positive in LELC (3), but is negative in lymphoepithelial sialadenitis (4). For patients with LELC of the parotid gland, it is important, however, to exclude a primary nasopharyngeal carcinoma because it is statistically more common to find a metastatic LELC than primary LELC in the parotid gland.

Our patient was found to have LELC involving the right parotid gland without a concurrent nasopharyngeal lesion. A previous series reporting nine Chinese patients with LELC of the salivary gland showed a predilection for female patients with a median age of fifty years. One-third of the patients in that series died within twenty-six months (5).

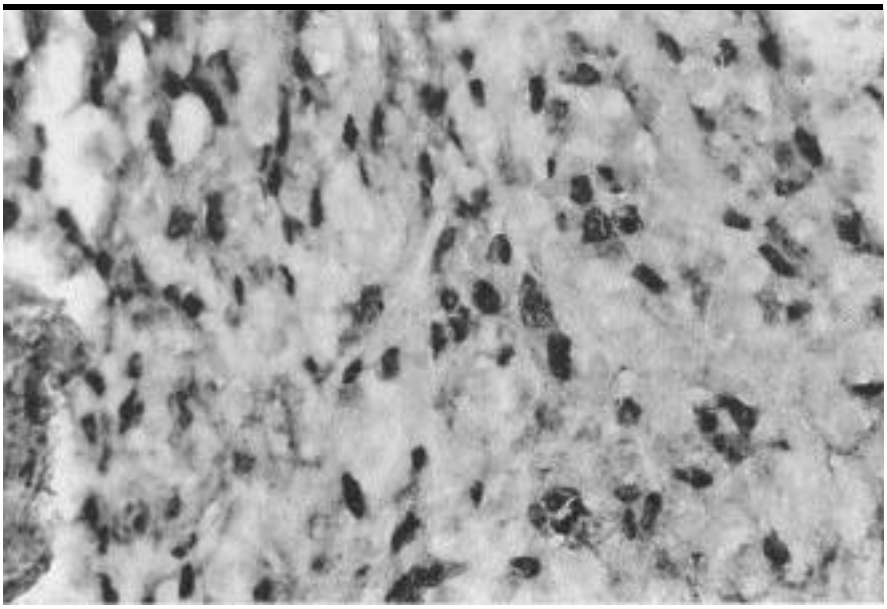

Fig. 2. *In situ* hybridization showing EBER in the nuclei of the tumour cells.

To our knowledge, there has not been any case report of LELC arising in patients with autoimmune diseases. All the 9 patients mentioned in the above series had no features suggestive of Sjögren's syndrome. It has been shown that patients with RA have an increased risk of developing malignancies, particularly EBV related lymphoproliferative disease (6). A case-control study by Baecklund *et al.* on a cohort of patients with RA showed that the increase in risk of lymphoma was related to RA disease regardless of drug treatment (7). On the other hand, although LELC has not been reported in post-transplant patients, EBV-related lymphoproliferative diseases have been well described after various immunosuppressive regimens involving different combinations of azathioprine, prednisolone, cyclosporine A and anti-thymocyte globulin (8). It is likely to be the degree of immunosuppression, rather than the particular regimen that is the most important predisposing factor. EBV-related lymphoma that developed in patients with RA has also been described in patients receiving long-term methotrexate (9). Our patient had been taking azathioprine for more than 10 years (cumulative dose 279.9 g) and it remains possible that long-term use of azathioprine confers immunosuppressive effect similar to methotrexate. A meta-analysis of articles published between 1966 and 1998 on the incidence of cancer in RA patients suggested the increase in risk of lymphoma was probably related to azathioprine use (10). Long-term azathioprine use alone (range of total cumulative doses of 89-260 g) has also been shown to induce acute myeloid leukemia in patients with autoimmune diseases (two systemic lupus erythematosus and one RA). Azathioprine is postulated to behave as a mutagen that leads to chromosomal aberrations involving the chromosome 7 (11).

In summary, we described here a patient with RA who had been receiving long-term azathioprine and was complicated by EBV-related LELC of the parotid gland. We also postulate the increase in risk of EBV-related malignancies may be related to the underly-

ing RA or immunosuppressive drug use, but additional studies are necessary to confirm or refute this hypothesis. Rheumatologists should nevertheless maintain a high index of suspicion for clinical manifestation of LELC as well as other lymphoproliferative disease in these patients. Pathologists should also be aware of this association, and not to misdiagnose LELC as lymphoepithelial sialadenitis. ISH study for EBER is helpful in this difficult differential diagnosis.

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