We present two patients with low-grade non-Hodgkin MALT lymphoma (mucosa-associated lymphoid tissue) occurring years before clinical evidence of autoimmune disorders. While the strong association between autoimmune disorders, in particular Sjögren’s syndrome and MALToma, is well described, the development of MALToma years before the onset of an autoimmune disease is very unusual. *Lupus* (2005) **14**, 551–553.

**Key words:** lupus erythematosus; MALT lymphoma

**Introduction**

Lymphomas originating in mucosal-associated lymphoid tissue (MALToma) are characterized by small B lymphocytes of low grade malignancy.

The commonest site for MALToma in humans is the gastrointestinal tract, specifically stomach, terminal ileum and appendix. They have also been described in the bronchus, salivary, thyroid and thymus glands. Conjunctival MALTomas as lymphomas are well described in the literature.1 Conjunctival MALToma is mostly a disease of the elderly with a mean age of diagnosis of 61 years.2 While not a common disease, its prevalence may be higher than previously recognized.3

DLE is a chronic condition characterized by cutaneous involvement. It occurs in between 5% and 20% of patients with SLE. Some patients with SLE have secondary Sjögren’s syndrome (SS), a chronic inflammatory autoimmune disorder characterized by lymphocytic infiltration of the exocrine glands.

The prevalence of SS in subjects with SLE ranges from 8% to > 30%4–6 and 80% of SS patients have a positive anti-nuclear antibody test. Anti-La antibodies occur in about 40% of patients and anti Ro antibodies in approximately 50% of patients. About 5% of patients with Sjögren’s (both primary and secondary disease) develop a lymphoreticular malignancy, most commonly a B-cell lymphoma,7 and the most common sites of MALToma in these patients is salivary glands and ocular adnexa.8

**Presentation of cases**

**Case 1**

A 28-year old woman presented with a two to three month history of painless swelling in the right eye. She had previously been in good health with no relevant family or past medical history. There were no visual symptoms. She had worn contact lenses since puberty. On ophthalmologic examination the visual acuity in both eyes was 6/6 with spectacles.

Slit lamp examination demonstrated large papillae on the tarsal conjunctiva and fornices of both eyes with some scarring of the left upper tarsal conjunctiva. There were also fairly prominent vessels at the limbus of the left eye. The rest of the ocular examination was unremarkable. Conjunctival biopsy showed a dense lymphoid infiltrate in the stroma and immunohistochemical stains revealed a mixture of polyclonal B-cells and T-cells. This appearance was that of reactive lymphoid infiltrate. The diagnosis was giant papillary conjunctivitis of uncertain aetiology possibly related to contact lens use. Topical steroid treatment and removal of contact lenses had resulted in improvement of the symptoms in one month. One year later the conjunctival lesion persisted and a new biopsy revealed a low grade non-Hodgkin lymphoma of the MALT type. The serum protein electrophoresis showed a monoclonal peak. There were no features of Sjögren’s syndrome, or lymphadenopathy and systemic examination was normal. CT scan of the orbits, chest and abdomen, blood tests and Immunoglobulin serum levels confirmed that the disease was localized.

The conjunctival lesion was treated with radiotherapy with complete remission after one course.
remains asymptomatic and there is no evidence of residual disease.

Twelve years later she developed biopsy proven discoid lupus on the eyelids and peri orbital area. Schirmer’s test was dry. All autoantibody tests were negative including ANA, all anti-ENA and anti-dsDNA antibodies, C3 and C4 levels were normal. The treatment was hydroxychloroquine at dose of 200 mg daily and topical treatment with a good response.

Case 2

The second case is a woman who, aged 41, developed swelling of the right parotid gland. The physical examination was otherwise normal and no other superficial lymphadenopathy was found. Biopsy of the parotid gland confirmed the diagnosis of MALToma. There was no evidence of systemic disease. The patient was treated with radio and chemotherapy with remission.

Four years later she presented with photosensitive skin rashes in the perioral area and on the V region of her neck, fatigue, polyarthritis and she reported dry mouth.

Autoantibody tests were positive for ANA, anti Ro, anti dsDNA and the level of C3 was low while the C4 was normal. The complete blood tests showed no other organ involvement. A diagnosis of SLE and secondary Sjögren’s syndrome was established. In addition, in view of three previous miscarriages and positive anti-cardiolipin antibodies she also has antiphospholipid (Hughes) syndrome.

The disease was well controlled initially with prednisolone and methotrexate and more recently with hydroxychloroquine 200 mg daily and aspirin 75 mg daily.

Comment

Several studies support a strong association between malignant non-Hodgkin’s lymphoma and Sjögren’s syndrome,10 autoimmune thyroiditis11 and autoimmune haemolytic anemia.12 The associations reported between non-Hodgkin’s lymphoma and systemic lupus erythematosus13 and rheumatoid arthritis are not as strong.14 Generally, autoimmune disease precedes lymphoma often by many years but in these two cases the lymphoproliferative disorder occurred several years before the manifestations of discoid lupus and Sjögren’s syndrome.

Sjögren’s syndrome is characterized by lymphocytic infiltration of exocrine glands, together with a polyclonal B-cell activation, as illustrated by the presence of multiple circulating autoantibodies against organ and nonorgan specific antigens.15

Sjögren syndrome patients have a greater tendency to develop a lymphoid malignancy. The risk of non-Hodgkin’s lymphoma (NHL) is estimated to be 44 times greater than in the normal population.10

The spectrum of lymphoproliferation extends from increased frequency of circulating monoclonal immunoglobulins and free light-chains, presence of mixed monoclonal cryoglobulinaemia, increased levels of circulating CD5-positive B-cells, to increased frequency of NHL.16–21 Some studies propose the term pseudolymphoma as an intermediate state between autoimmunity and malignant lymphoma.9 Pseudolymphoma probably corresponds to low-grade B-cell lymphoma. Chronic stimulation by exoantigen or autoantigen play an important role in developing these tumors, by driving the proliferation of specific B-cells and by increasing the frequency of their transformation. Predictive factors of lymphoma development are lymphadenopathy, splenomegaly and parotid gland enlargement.10 Previous low dose irradiation or chemotherapy may lead to an increased risk of lymphoma. One study found that the presence of mixed monoclonal cryoglobulins is the most significant risk factor in predicting the risk of lymphoma development,22 but neither of our patients has a cryoglobulin.

In summary, these two case reports of MALT lymphoma preceding the onset of an autoimmune disorder raise interesting questions about the relationship of lymphoma to autoimmunity.

References

11 Ansell SM, Grant CS, Habermann TM. Primary thyroid lymphoma. Semin Oncol 1999; 26: 316–323.