

Prognosis and long-term outcome in primary Sjögren's syndrome

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The course of primary Sjögren's syndrome (SS) may be complicated by the development of extraglandular involvement and organ specific autoimmune disease. In contrast, the long-term course of tear gland function in patients with primary SS is characterised by a steady state situation (1).

In a longitudinal study following 100 patients with primary SS for a median of 34 months (range 3-84 months), three patients developed malignant lymphoma. Other complications included pericarditis (10%), pleuroparenchymal lung disease (9%), renal tubular acidosis (3%), and cerebrovascular accidents (2%). Severe systemic disease was associated with the presence of anti-Ro/SSA antibodies (2).

In a long-term follow-up after 10-12 years, only 4 of 31 patients with primary SS developed new features related to autoimmune disease, not necessitating treatment with corticosteroids. None of the patients developed major glandular complications. However, three of these patients with primary SS developed malignant lymphoma (3).

After a 2 year follow-up, 18 non-smoking women suffering from primary SS were re-examined extensively, including pulmonary function tests (PFT), bronchoalveolar lavage (BAL) and high-resolution computed tomography (HRCT). PFT revealed unchanged values. Five of 18 patients had abnormal HRCT, and all these patients had abnormal BAL (4). The absence of major changes in PFT was confirmed in another longitudinal study (5).

In a retrospective, long-term observational clinical study, a new model for classification of disease manifestations in primary SS was evaluated. Plasma level of IgG, serum level of antinuclear antibodies and assessment of focal sialadenitis in labial salivary gland biopsy specimen were used as markers for immunoinflammatory activity. Pulmonary infiltrates and fibrosis, renal tubular acidosis, purpura, myositis, Raynaud's phenomenon and haematological cytopenia were associated with high levels of at least one of the three markers mentioned. The baseline markers of disease activity were observed to be correlated with the long-term outcome of clinical disease (6).

Since the first report of an increased incidence of malignant lymphoma in patients with Sjögren's syndrome (SS) multiple examples of this association have been described and primary SS is often considered to be a link between autoimmune and lymphoproliferative disease (7-11). In an epidemiological study the risk of malignant lymphoma for patients with SS was 6.4 cases per 1000 per year (8). In a retrospective cohort study of 55 primary SS patients we followed 8-18 years: five patients developed malignant lymphoma (12). In a long-term follow-up of 10-12 years 3 of 30 patients with primary SS died from malignant lymphoma and one other patient had developed benign IgM-kappa paraproteinemia (3). Although a similar risk for primary and secondary SS was reported (8), lymphoma is believed to be more common in primary SS (10).

The proportion of patients with SS who develop malignant lymphoma varies from 4-9% in several studies. This variation may result from the different criteria used for the diagnosis of SS. It may also be due to differences in length of follow-up.

Although some clinical signs may forebode the onset of lymphoma, there are few laboratory markers that will be able to identify patients who are at risk for the development of malignant lymphoma.

Usually, SS patients who develop lymphoma have several features of generalised, extraglandular disease (7). In a retrospective cohort of 55 patients with primary SS, hyperglobulinemic purpura on the legs was seen in three of five patients who developed lymphoma (12). In addition, in other studies also patients with isolated sicca syndrome were followed, none of these patients developed malignant lymphoma (3,12). Parotid gland enlargement, lymphadenopathy, and previous exposure

to cytotoxic agents have also been reported as predictive factors for the development of malignant lymphoma in SS (8). Patients with SS who develop lymphoma may reveal a decrease in autoantibodies, and longstanding hypergammaglobulinemia may turn into hypogammaglobulinemia leading to immunodeficiency and lowered resistance to bacterial infections (10,13).

In three of ten patients with SS with monotypic plasma cell populations in labial salivary gland tissue, defined by a kappa:lambda ratio of >3 , progression to systemic monoclonal lymphoproliferative disease was observed (14). Consequently, quantitative immunohistological examination of labial salivary gland biopsy specimens might select patients with SS at risk at the time of biopsy. Also immunoglobulin heavy chain monoclonality in labial salivary gland biopsies has been suggested to be a relatively common finding in patients with SS, which may prove to be a useful marker for the development of lymphoma (15).

Recently, it was reported that the presence of mixed monoclonal cryoglobulinemia (MMC) is significantly correlated with an increased frequency of extraglandular manifestations in primary SS. During a five-year period, 7 of 18 patients with primary SS with MMC developed lymphoma. Six of these 7 (86%) patients had MMC before the appearance of lymphoma, compared with 12 of 96 (12.4%) of the patients who did not develop lymphoma. Monoclonal rheumatoid factor associated cross-reactive idiotypes were also correlated with lymphoma development (16).

Although, in general, primary SS may be characterised by relatively stable course, an increased risk for manifestations of organ specific and generalised autoimmune disease, and an increased risk for the development of malignant lymphoma, necessitate a confirmation of a presumptive diagnosis of primary SS.

In conclusion, discrepancies of the frequency of complications, including extraglandular involvement and organ specific autoimmune disease, and the development of malignant lymphoma, may result from the different criteria used for the diagnosis of Sjögren's syndrome. The main problem encountered in epidemiology remains the lack of an uniformly accepted disease classification system.

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