B Cells Raise Rheumatoid Titers

Sjögren's *from page 1*

Among the 272 patients, 59 (22%) had morphologic evidence of germinal centers present, as did 47 (28%) of the 169 patients who met the full revised international criteria for primary Sjögren's syndrome. The current diagnostic criteria require both objective and subjective evidence of salivary gland and ocular involvement, as well as the presence of anti-Ro and/or anti-La in serum.

Additionally, 60 biopsy specimens chosen randomly were further investigated with immunohistochemistry, and germinal center–like features were identified in 18 (30%).

"Irrespective of the method used to detect germinal centers, the mean inflammatory focus scores were significantly increased in the germinal center–positive patients," Dr. Jonsson wrote.

Among patients who were germinal center positive, titers of rheumatoid factor were higher than among those who were germinal center negative, and serum autoantibody and IgG levels were increased as well.

There also is evidence that the presence of these B-cell–containing structures may predict subsequent lymphomatous transformation and the development of B-cell non-Hodgkin's lymphoma.

"We therefore suggest that ectopic germinal cell formation should be considered in the diagnostic evaluation of Sjögren's syndrome as it may be related to the increased risk of developing extraglandular disease," Dr. Jonsson wrote.

The finding that B cells may play an important role in Sjögren's syndrome also has implications for treatment. Conventional treatment of the syndrome involves symptomatic management of dry eyes and mouth, as well as immunosuppressive agents such as azathioprine in cases with severe complications such as vasculitis and pulmonary or renal damage.

But targeting the CD20 antigen on the surface of B cells with rituximab offers a new approach, Dr. Jonsson said.

The drug has been tested in a small phase II study that included 15 patients, 8 of whom had early primary Sjögren's syndrome and 7 who also had mucosa-associated lymphoid tissue lymphoma. All patients had elevated IgG levels, had anti-Ro and anti-La autoantibodies, and were positive for IgM rheumatoid factor. The patients with lymphoma were stage IE, localized to the parotid glands, and had longer disease duration and less residual salivary function.

They were given four weekly infusions of rituximab, 375 mg/m^2, after intravenous pretreatment with 25 mg prednisone and 2 mg clemastine to prevent infusion reactions.

The patients with early Sjögren's syndrome reported subjective improvements in their symptoms, and objective immunologic analyses found a decrease in B cells and normalization of IgG levels.

Complete remission was achieved in three of the patients with lymphoma, while disease remained stable in three and progressed in one (Arthritis Rheum. 2005;52:2740-50).

But further investigation will be needed with regard to safety.

Rituximab is a chimeric monoclonal antibody, and four of the patients developed human antichimeric antibodies.

Three developed serum sickness–like disorder, which had not previously been reported with rituximab. ■

Young Age, Mucosal Involvement Predict Relapses in Pemphigus

BY NANCY WALSH
New York Bureau

SORRENTO, ITALY — Patients with pemphigus who are younger than 40 years at the time of diagnosis and whose first remission is brief are likely to have a more severe course of disease and multiple relapses, Dr. David Mimouni said at the Fifth International Congress on Autoimmunity.

Much remains unknown about the natural history of pemphigus. In an attempt to address this, a survey was undertaken of 155 patients diagnosed with some form of pemphigus and treated at an Israeli center between 1976 and 2004.

Follow-up for the patients ranged from 4 to 28 years. Of these patients, 94 were female. The age distribution at disease onset was typical of pemphigus, peaking between 40 and 50 years, said Dr. Mimouni of the department of dermatology, Rabin Medical Center, Petah Tiqwa, Israel.

Pemphigus vulgaris was the diagnosis in 144 patients. The remainder had diagnoses of pemphigus foliaceus, in which only the skin is involved and the mucous membranes are spared; pemphigus erythematosus, with features of both pemphigus and lupus; and paraneoplastic pemphigus.

In only 16 patients could a precipitating factor such as stress, drugs, or sun exposure be identified, he said.

The initial site of involvement was the mucosa alone in 50%, the skin alone in 47%, and both in 3%. At the time of follow-up, however, involvement limited to the mucosa or skin was seen only in 21% and 24%, respectively, while both sites were affected in 55%, Dr. Mimouni said.

A total of 91 patients were of Ashkenazi Jewish origin, while 58 were of Sephardic origin, and 6 were Arab. At the time of follow-up, the Sephardic patients were significantly less likely to be in remission than were the Ashkenazi, which was surprising, because a strong genetic link had previously been established for Ashkenazi origin, Dr. Mimouni said.

Younger patients and those whose initial remission lasted less than a year also were less likely to be in remission at the time of follow-up, as were those with mucosal involvement.

All patients had been treated with high doses of steroids, usually between 1.5 and 2 mg/kg per day, for periods up to 10 years. Most also had adjuvant therapy, most commonly with azathioprine, although recently other agents such as mycophenolate mofetil had been used.

Only 2% of the study patients had never had a relapse following treatment, while 40% had one to two relapses, and 58% had more than three, he said.

A total of 16 patients died. The causes of death were cancer, ischemic heart disease, and pulmonary embolism. None of the deaths was directly related to pemphigus, which represents a marked change from 1950, when 90% of patients would have died of pemphigus within 2 years, Dr. Mimouni said.

This study suggests that although there still is no cure for pemphigus, the morbidity and mortality associated with the disease have decreased significantly.

Progress has also been made in deciphering some of the underlying autoimmune processes in these conditions. For example, it is now known that pemphigus vulgaris is characterized by the presence of antibodies to desmoglein 1 and 3, which are adhesion molecules located between epidermal cells. Targeting these desmosomal antigens results in the loss of adhesion between keratinocytes, causing erosions and blisters, Dr. Mimouni explained. ■

SLE Patients at High Risk for Non-Hodgkin's, Other Cancers

BY NANCY WALSH
New York Bureau

SORRENTO, ITALY — Patients with systemic lupus erythematosus are at high risk for the development of certain types of malignancy, particularly non-Hodgkin's lymphoma and cervical cancer, Dr. Emese Kiss said at the Fifth International Congress on Autoimmunity.

Improved treatments have resulted in greater life expectancy among patients with lupus, with the unintended consequence that morbidity and mortality from causes other than lupus itself have assumed increasing importance.

A retrospective analysis of data from 860 patients seen between 1970 and 2004 identified 37 cases of cancer, for an overall prevalence of 4.3%, reported Dr. Kiss of the University of Debrecen (Hungary).

When compared with age- and sex-matched controls, the resulting standardized incidence ratio for all cancers of 0.85 was not elevated, she said.

But the standardized incidence ratios for cervical cancer, hematologic malignancies, and non-Hodgkin's lymphoma were 1.74, 1.31, and 3.47, respectively.

The highest relative risks were 4.6 for non-Hodgkin's lymphoma and 2.3 for cervical cancer, she said.

During the study period 164 patients died, 18 of malignancies, for a cancer-related mortality of 11%.

In most other surveys of cancer among patients with lupus, elevated risks have been reported for lung, hepatobiliary, and hematologic malignancies. Some studies also have found increased frequency of breast, gynecologic, bladder, and prostate cancer, depending on age, race, and gender distribution.

Among the postulated reasons for the increased lymphoma risk in lupus patients are high inflammatory activity and uncontrolled B-cell proliferation, which increase the risk of oncogene translocations, Dr. Kiss explained in an interview.

Diffuse, large B-cell lymphomas that are derived primarily from peripheral activated B cells are the major types of lymphoma in patients with lupus as well as in those with rheumatoid arthritis. This can be considered indirect evidence supporting the role of inflammation and disease activity in the development of non-Hodgkin's lymphoma, she said.

The use of immune modulatory agents in treatment also may contribute, either by direct mutagenesis or by disturbing immune surveillance and thus allowing dysregulated proliferation of B cells, she said.

Another contributing factor may be the fact that lupus and non-Hodgkin's lymphoma share some clinical manifestations, including thrombocytopenia, leucopenia, anemia, lymphadenopathy, and hepatosplenomegaly. This may complicate and delay the diagnosis of non-Hodgkin's lymphoma.

The elevated risk for cervical cancer may relate to increased rates of infection with human papillomavirus or to impaired clearance of the virus. It also may be associated with the use of cytostatic drugs, although a direct association between human papillomavirus infection and treatment with cyclophosphamide or azathioprine could not be confirmed, Dr. Kiss said.

An important implication of these data is that increased attention must be paid to screening for these cancers, such as with Pap testing, she said.

An additional "surprising" finding in this analysis was that the malignant disorders appeared not as late complications, but most often within the first 5-10 years after the onset of lupus. "This suggests that immune suppressive therapy is not the only factor increasing cancer risk, and again supports the importance of high disease activity in the development of cancer," she said.

The mean age at the onset of malignancy was 47 years. The earliest malignancies to develop were the hematologic and hepatobiliary cancers, while colorectal and gastric cancers appeared much later, sometimes more than 20 years after the diagnosis of systemic lupus erythematosus, Dr. Kiss said. Half of lupus patients do not survive long enough to develop gastrointestinal cancers, she said. ■