Rheumatoid arthritis and B-cell chronic lymphocytic leukemia

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ABSTRACT

The association between lymphoproliferate malignancies, especially lymphoma, and rheumatoid arthritis (RA) has been confirmed by several studies. However, there are few reports of RA patients who developed B-cell chronic lymphocytic leukemia (B-CLL) and vice versa. We report a patient with B-CLL who developed RA and another with RA who presented with B-CLL during follow-up. We discuss the incidence of B-CLL among the RA population and the possible interaction of the pathogenetic mechanisms of these two entities.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease of unknown etiology characterized by symmetric erosive arthritis of the diarthrodial joints as well as extraarticular manifestations (1). Chronic lymphocytic leukemia is a clonal malignancy of the B lymphocytes characterized by progressive accumulation of long-lived small lymphocytes, and is manifested clinically by immunosuppression, bone marrow failure, and organ infiltration with neoplastic cells, as well as autoimmune phenomena (2). The association between lymphoproliferative malignancy and RA has been confirmed by case control studies, population surveys and investigations of the rheumatoid population (3,4). To date, there are few reports of RA patients who developed B-cell chronic lymphocytic leukemia (B-CLL) (5), while most lymphoproliferative malignancies occurring in RA patients are lymphomas (3).

We describe two patients with the coexistence of RA and B-CLL and discuss the possible interaction of the pathogenetic mechanisms of these two entities.

Methods

The number of patients with RA attending the outpatient Rheumatology Clinic in Northwest Greece during the period 1994-2000 was 498. Two patients with B-CLL were hospitalized at the University Hospital of Ioannina. The first was a man with symptoms of fatigue and loss of appetite. The second patient was a woman who presented with symmetrical arthritis. They underwent a physical examination; a complete blood count with differential and

Table I. Clinical features and diagnostic criteria of rheumatoid arthritis and B-cell chronic lympocytic leukemia patients.

Criteria	Patient 1	Patient 2
ACR		
Morning stiffness	yes	yes
Arthritis of 3 or more joints	yes	yes
Arthritis of hand joints	yes	yes
Symmetric arthritis	yes	yes
Rheumatoid nodules	no	no
Serum rheumatoid factor	negative	positive
Radiological changes	yes	yes
B-CLL		
White blood cell count $x10^9$/L	25 (13.8)	18 (24.7)
Lymphocytes (%)	74 (70)	78 (62)
Flow cytometry from peripheral blood (%)		
CD_5^+ CD_{20}^+	50	73
CD_5^+ CD_{23}^+	50	73
CD_{19}^+ HLA-DR^+	50	73
CD_{22}^+ k^+dime	23	no
CD_{16}^+ CD_{56}^+	4	7
Bone marrow lymphocytic inflitration (%)	60	30

ACR = American College Rheumatology (7); B-CLL = B-cell chronic lympocytic leukemia (6).

platelet counts; and routine laboratory tests including urine analysis, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). In addition, tests for viruses including antibodies to human T-lymphotropic viruses (HTLV) I and II were performed, as well as immunological tests such as rheumatoid factor (RF) and antinuclear antibodies (ANA). Finally, flow cytometry of the peripheral blood; a tuberculin skin test; chest, wrists and hands roentgenograms; and chest and abdominal computer tomograph scans (CT) were performed.

Patient 1

A 72-year-old man was hospitalized in November 1993 because of fatigue and loss of appetite for the last 3 months. His physical examination was unremarkable. Chest x-ray as well as CT of the chest and abdomen were normal. Laboratory evaluation revealed leukocytosis $25x10^9$/L with 74% morphologically mature lymphocytes. The diagnosis of B-CLL Rai staging 0 was made by flow cytometry of the peripheral blood and a bone marrow biopsy (6) (Table I). The patient received no therapy.

In January 1994 he was re-admitted to our hospital because of morning stiffness and symmetrical polyarthritis. Physical examination revealed swelling and tenderness of the metacarpophalangeal joints (MCP), wrists, elbows, ankles and knees. Hand and wrist x-rays showed extraarticular osteoporosis, slight cartilage destruction and joint space narrowing of the 2nd, 3rd and 4th MCP joints bilateraly. The peripheral blood count revealed leukocytosis 25 x 10^9/L with 70% lymphocytes and anemia of chronic disease (low serum iron and normal ferritin) with hemoglobin 11.5 g/dl. The ESR was 80 mm/h and the CRP 96 mg/dl. Rheumatoid factor was negative. HTLV I/II were also negative. Serum protein electrophoresis disclosed no monoclonal bands. There were no symptoms or signs of Sjögren's syndrome (SS).

The diagnosis of RA was made according to the American College of Rheumatology (ACR) criteria (7) (Table I) and he was treated with small doses of prednisone (7.5 mg per day) and methotrexate (MTX) 15 mg per os/week. In March 2000 the patient had 13.8 x 10^9/L leukocytes (with 70% lymphocytes) and his arthritis was in remission on maintenance therapy with MTX and no steroids.

Patient 2

A 60-year-old woman with a long history of RA since 1987 presented in January 1997 to our outpatient Rheumatology Clinic for evaluation. She complained of morning stiffness and physical examination revealed symmetric arthritis involving the small joints of the hands and wrists bilaterally. Laboratory evaluation revealed a normal peripheral white blood count and differential, high titer of RF (1/320). The serological tests for HTLV I/II were negative. Hand and wrist x-rays revealed juxtraarticular osteoporosis with subcondral bone destruction of the MCPs joints (1st, 3th) bilaterally, as well as small cysts of both styloids. The diagnosis of RA was confirmed (7) (Table I). The patient complained of dry eyes. However, objective studies for sicca syndrome and minor salivary gland biopsy were within normal limits. The patient was treated with MTX (12.5 mg per os/week) and prednisone (7.5 mg per os/day). One year later, during a regular follow-up the peripheral blood count showed leukocytosis $18x10^9$/L with 78% mature lymphocytes. Bone marrow biopsy and peripheral blood flow cytometry confirmed the diagnosis of B-CLL Rai staging 0 (6) (Table I). Serum protein electrophoresis showed no abnormalities. In February 2000 the peripheral leukocytes was $24.7x10^9$/L with 62% lymphocytes and her arthritis was in remission.

Results

Among 498 RA patients seen over a 6-year period at our outpatient rheumatology clinic, 2 manifested B-CLL. In the first patient the B-CLL preceded the diagnosis of RA, while the second followed its diagnosis. In Table I we present some features of the RA/B-CLL patients. The B-CLL was low grade, requiring no treatment, while the RA disease was treated with MTX and small doses of prednisone.

The 7-year incidence of B-CLL in our RA population was approximately 4 cases/1,000 patients. The incidence of B-CLL in our country is not yet known with precision. However, according to the American Cancer Society the 7-year incidence of B-CLL in the general population is approximately 0.2 cases/1,000 individuals. Therefore, it seems that B-CLL among our RA population was higher than in reports for the general population.

Discussion

In the present study two cases of RA/B-CLL are reported. It is obvious that the 7-year incidence of B-CLL in our RA patients was increased compared to the general population. Our results are in agreement with those reported by Taylor *et al.* who described 4 cases of B-CLL among 1,505 RA patients (5).

Patients with RA have a disproportionate tendency to develop lymphoproliferative disorders. The spectrum of lymphoproliferation extends from an increased frequency of Hodgkin's disease, non-Hodgkin's lymphoma, myeloma, acute leukemia and B-CLL (3-5, 8). Various hypothesis explaining the above disorder have been postulated: 1) proliferation of a forbidden clone of lymphocytes producing both diseases, 2) susceptibility in both diseases due to a genetic predisposition or a single causative agent such as a virus, 3) the increased expression of oncogenes, 4) chronic immune stimulation causing malignant transformation of B-cell lines, and 5) treatment of RA with immunosuppressive drugs leading to lymphoproliferation (8).

Concerning the first hypothesis of a forbidden clone of lymphocytes causing both disorders, the relatively long period between the onset of RA and the development of B-CLL in the second patient in our study makes this possibility unlikely. The concept of a single causative agent such a virus producing both diseases is also unlikely, since both patients were negative for HTLV-I and -II viral infection, which may be implicated in the pathogenesis of both diseases (9). Another theory applying

the concept of ongogene activation has been proposed to explain the relationship between autoimmunity and malignancy. Oncogenes are normal genes, but when they are overexpressed their regulation is altered, or a mutation occurs inducing a structural change, and neoplastic transformation may result. Increased expression of c-myc, c-myb and c-ras was detected in the lymphocytes of patients with autoimmune diseases compared to normal individuals (10). The risks of therapy causing lymphoproliferation in RA are the subject of considerable debate. We found no possible evidence to implicate therapy as a cause of B-CLL, since none of our patients had been treated with cytotoxic drugs (11).

Thus, the most likely cause of lymphoproliferation in RA might be chronic immune stimulation. There are some findings to support this hypothesis:

a) The potential of chronic immune stimulation to induce malignant transformation of B-cells is well demonstrated in SS patients (12, 13). Neither of our patients, however, presented with such a disorder. Nevertheless, the transition from polyclonal lymphoid hyperplasia to a monoclonal proliferative disorder may be further enchanced by decreased immune surveillance resulting from the impaired B and T cell functioning which is present in SS, RA and other autoimmune diseases (14, 15).

b) Another finding supporting chronic immune stimulation and the transition to malignant transformation is the role of CD5+ B-cells. The CD5+ B-cell population is prominent in early life and produces low activity and thereby polyreactive antibodies. The question as to whether CD5 is a marker of activation or a molecule specific for a B-cell lineage remains unresolved. Studies by P. Youinou *et al*. suggest the possibility of a different type of CD5+ B-cells. Indeed, activated CD5+ B-cells do proliferate following CD5+ engagement, while resting CD5+ B-cells do not (16). CD5+ B-cells occur in abnormally high concentrations in the peripheral blood and synovial fluid of RA (17, 18) and other autoimmune patients (19). On the other hand, the B-cells of most of the CLL express CD5+ molecules (20). CD5+ B-cells seem to be involved in autoantibody production in autoimmune diseases and are particularly susceptible to transformation in lymphoproliferative disorders. Thus, this B-cell population appears to play a key role in the crossing of non-organ specific autoimmune diseases and lymphoproliferative disorders.

c) Finally, another point to take into consideration in this setting is the NK hypothesis. NK cell activity is thought to be an important immune surveillance mechanism against malignancy (21). Natural killer cell activity has been shown to be reduced in the peripheral blood, synovial tissue and synovial fluid of RA patients (5). Both of our patients had a decreased number of NK cells in their peripheral blood. Thus, the reduced NK cell activity in patients with active RA may allow CD5+ B-cells to proliferate and spill over into the circulation as well as to undergo spontaneous malignant transfunction.

We conclude that RA patients may develop B-CLL during follow-up and conversely B-CLL patients may present findings of RA. Thus, lymphocytosis in RA patients should be thoroughly investigated. Since the etiology of RA is multifactorial, it is likely that many factors may be responsible for the link between RA and lymphoproliferative disorders.

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