Multiple Myeloma Occurring in Early Stage Primary Biliary Cirrhosis

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B-cell neoplasms are not infrequently associated with autoimmune diseases. A 60-year-old man with multiple myeloma developing in an early stage primary biliary cirrhosis was reported. Initially, he had hypergammaglobulinemia with monoclonal gammopathy (IgG-x type), elevation of serum IgG and IgM, and positive serum antimitochondrial antibodies. There were compression fractures of the lumbar vertebrae, where bone marrow aspiration revealed proliferating myeloma cells. Liver biopsy revealed destruction of bile duct surrounded by an inflammatory infiltrate, which was consistent with stage I primary biliary cirrhosis. The association suggested the role of immunoregulatory abnormalities in the development of multiple myeloma.

CASE REPORT

The patient, a 60-year-old man who had been admitted to a local hospital with pneumonia, was referred to us for evaluation of hypergammaglobulinemia and mild liver dysfunction.

On admission the patient was afebrile and slightly hypertensive. Laboratory studies

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showed an erythrocyte count of 411 x 10^4/mm³, hemoglobin 12.9 g/100 ml, leucocyte count 6.7 x 10^9/mm³, platelets 267 x 10^9/mm³, and an erythrocyte sedimentation rate of 72 mm/hr. The coagulation profile was normal. BUN, creatinine and plasma electrolytes were normal. The serum total bilirubin was 0.6 mg/100 ml (normal: 0.3-1.1). The serum alkaline phosphatase was 371 U/liter (normal: 98-279), the γ-glutamyl transpeptidase 58 U/liter (normal: 11-51), and the leucine aminopeptidase 71 U/liter (normal: 21-58), while the serum transaminases were within normal limits. The total plasma protein was 9.4 g/100 ml with an increase in the γ-globulin fraction (3.4 g/100 ml), which revealed an M protein spike on electrophoresis. Immunoglobulin concentrations were: IgG 3,710 mg/100 ml, IgA 850 mg/100 ml, and IgM 360 mg/100 ml. Immunelectrophoresis demonstrated a monoclonal component of IgG-κ. Tests for antinuclear antibody and anti-DNA antibody, as well as LE cells were negative, while the antimitochondrial antibody test was positive at a titer of 1:360. A bone marrow aspiration revealed plasma cell proliferation (17.4%), however, these cells were not thought to be myeloma cells, but rather a reactive proliferation. Urinary excretion of Bence-Jones protein was negative. A bone survey revealed osteopenia and mild deformity of the vertebrae. The liver biopsy showed a small foci of inflammatory cell infiltrate, single cell necrosis in the liver parenchyma and mild infiltration of mononuclear cells in the sinusoids. Although the portal tracts were mildly infiltrated with inflammatory cells, the limiting plates of the parenchyma were almost normal. Bile duct lesions were not conspicuous in this specimen (Fig. 1).

Two years later the patient got a contusion on his chest by accidentally falling down the stairs. Radiographs revealed fracture of the sixth rib. He also had complaint of back pain and of difficulty in walking. Radiographs of the vertebral column revealed severe osteopenia, deformity, and compression fractures in the lumbar spine (Fig. 2), and atypical lytic lesions were seen in the skull. A bone marrow aspiration showed increased numbers of pleomorphic plasma cells (21.4%) with frequent mitoses and multiple nuclei, compatible with a diagnosis of multiple myeloma (Fig. 3). A liver biopsy showed that the limiting plates were partially disrupted. Proliferation of bile ductules was not seen in the biopsy specimen (Fig. 4). Inflammatory infiltrate, predominantly composed of lymphocytes and

Fig. 1. Liver biopsy specimen at the first admission. Bile duct lesions are not conspicuous.
(Hematoxylin and eosin, original magnification ×100)
histiocytes, surrounded bile ducts in expanded portal areas, and destruction and rupture of the bile ducts were commonly seen (Fig. 5). These findings were interpreted as stage I primary biliary cirrhosis according to the criteria of Scheuer (1980).

In liver function tests, the serum alkaline phosphatase and the \( \gamma \)-glutamyl transpeptidase were elevated to 481 U/liter (normal: 105-262) and 110 U/liter (normal: 5-42), respectively, much higher than at the previous admission. The serum total bilirubin and

Fig. 2. Severe osteopenia, deformity, and compression fractures were seen in the lumber vertebrae.

Fig. 3. A bone marrow aspiration showing proliferation of pleomorphic plasma cells with multinuclei, a finding consistent with multiple myeloma.

(May-Giemsa stain ×1,000)
the serum transaminase were normal. The total plasma protein was 9.4 g/100 ml and the γ-globulin fraction was 3.8 g/100 ml. On immunological studies, peripheral blood lymphocyte analysis showed that the proportion of T cells was 91% and that of B cells was 4%. T lymphocyte subset analysis showed a ratio of CD4/8 of 3.62 (normal: 0.6-2.9). HLA-DR and IgG FcR positive T cells were in the normal range. Natural killer cell activity was 47% (normal: 18-40). Blastoid transformation for phytohemagglutinin (PHA) and concanavalin A (Con A) were normal. C3 was 140 mg/100 ml (normal: 66-140) and C4 was decreased to 9.6 mg/100 ml (normal: 12-34). CH50 was normal.

Fig. 4. Liver biopsy specimen at the second admission. An appearance interpreted as stage I primary biliary cirrhosis. (Hematoxylin and eosin, original magnification x40)

Fig. 5. Liver biopsy specimen at the second admission. Destruction and rupture of bile ducts surrounded by inflammatory infiltrates in the expanded portal area. (Hematoxylin and eosin, original magnification x200)
Rheumatoid factor was positive at 1410 IU/100 ml (normal: <30) as was antimitochondrial antibody at a titer of 1:160. Sjögren's or sicca syndrome was not found. Thyroid functions were normal. Hepatitis B surface antigen and hepatitis C antibody were negative.

An intermittent course of melphalan and prednisone was started. Twelve such courses had been given to the patient during one year, resulting in a decrease in myeloma cells in the bone marrow specimen and an improvement in several immunological parameters. The patient occasionally suffers from back pain and bone aches, but has been and is treated as an ambulatory patient.

**Discussion**

The association of multiple myeloma with primary biliary cirrhosis has rarely been observed and only a few cases were reported (Bladé et al. 1981; Fujii and Yashige 1989). This association appears to be related to an abnormality in the interaction between T and B cells. A decreased suppressor T-cell function in patients with primary biliary cirrhosis has been observed in several in vitro studies. One study suggests that the primary abnormality in immunoglobulin production is the result of defective suppressor T-cell function which fails to inhibit immunoglobulin synthesis due to unregulated B-cell function (James et al. 1980). In vitro studies on the mechanism of increased serum IgM levels in primary biliary cirrhosis suggest that the main suppressor cell abnormality more affects the regulation of IgM secretion by B-cells, than causes B-cell proliferation (Nouri-Aria et al. 1985). Another study on the state of B-cell activation in patients with primary biliary cirrhosis demonstrates that the humoral abnormalities specific to this disease are attributable to the activation of a small subpopulation of B-cells rather than to generalized B-cell hyperactivity, while the majority of circulating B-cells were not activated (James et al. 1985). In primary biliary cirrhosis it is generally recognized that B-cell hyperactivity enhancing the production of immunoglobulin or autoantibodies is related with impeded regulatory function on the part of T-cells.

B-cell hyperactivity characterized by excessive production of immunoglobulin and autoantibodies is also observed in other autoimmune diseases. In rheumatoid arthritis and systemic lupus erythematosus, B-cell hyperactivity, probably due to impairment of suppressor T-cell activity, has been demonstrated (Alpert et al. 1987). Although B-cell hyperactivity has also been demonstrated in Sjögren's syndrome, an attempt to explain this from T-immunoregulatory subset function was not successful (Moutsopoulos and Fauci 1980). In autoimmune diseases, decreased suppressor T-cell function does not appear to be the sole factor of B-cell hyperactivity, and some stimulating factors may also be involved. Furthermore, for the development of B-cell neoplasm from activated B-cells, some factors are thought to be necessary for the promotion of proliferation, clonal expansion and neoplastic growth of B-cells. A study on the incidence of malignant neoplasms among patients with rheumatoid arthritis disclosed that
lymphoma, leukemia and myeloma develop more frequently than in the general population, with a difference statistically significant (Isomäki et al. 1978). Plasmocytic dyscrasias are frequently seen in patients with rheumatoid arthritis (Wegelius et al. 1970). These clinical experiences in rheumatoid arthritis suggest that a continuous immunological stimulation may probably leads to proliferation and malignant transformation of some clones of lymphocytes. Sjögren’s syndrome, where the lympho-proliferating lesion ranges over a dynamic spectrum from benign polyclonal lymphoid hyperplasia to malignant lymphoma with monoclonal characteristics, is an ideal model for the study of the pathogenesis of both autoimmunity and malignancy. Recently, an autocrine growth factor contributing to lymphoproliferation was identified from a B-cell line established from a patient with Sjögren’s syndrome (Takei et al. 1989). Inappropriate production of autocrine growth factor and of other lymphokines known as B-cell growth and differentiation factors may also contribute to the development of B-cell malignancy.

The association of primary biliary cirrhosis with B-cell neoplasms has sporadically been reported. In these, multiple myeloma (Bladè et al. 1981; Fujii and Yashige 1989) or malignant lymphoma (Ijichi et al. 1987) were associated. We assume that the mechanisms involved in the development of B-cell neoplasm in these cases have also played some role in the present case. Of course, we cannot conclude a positive correlation between primary biliary cirrhosis and multiple myeloma from a small number of cases. However, studies should be extended toward the pathogenesis of this association: It will be helpful to elucidate not only the mechanisms of autoimmunity in primary biliary cirrhosis, but also those involved in the malignant growth of plasma cells in this disease.

References


