

HEPATOPANCREATOBİLİER

Monoclonal Gammopathy in Liver Cirrhosis: A Report of Nine Cases

KARACİĞER SİROZUNDA MONOKLONAL GAMMOPATİ:
9 VAKANIN GÖZDEN GEÇİRİLMESİ

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SUMMARY

Monoclonal gammopathy was detected in sera of nine patients with liver cirrhosis but no evidence of lymphoproliferative disorders. The type of M-protein was IgG kappa in four, IgM lambda in three and IgA kappa in two patients. Only one patient had Bence-Jones proteinuria. In all patients, the percentage of plasma cells in bone marrow was less than 5% (between 1 and 3%). Serum B-2 microglobulin levels were not elevated, and four patients except one had normal concentrations of serum immunoglobulins. Clinical and laboratory findings of four patients who were followed by 6-24 months remained stable.

Key Words: Liver cirrhosis, Monoclonal gammopathy

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The monoclonal gammopathy which is characterized by proliferation of a single clone of plasma cells that synthesis a homogenous, monoclonal protein (M-protein) may occur in different disorders. The monoclonal gammopathies are clinically classified into monoclonal gammopathy of undetermined significance (MGUS), malignant monoclonal gammopathy (multiple myeloma, Waldenstrom's macroglobulinemia), heavy chain disease, cryoglobulinemia and primary amyloidosis (1). MGUS is used to define the monoclonal gammopathy which occurs in patients without neoplastic disease of B lymphocytes. Although many different terms such as essential, benign, idiop; ic, asymptomatic, nonmyelomatous and discrete monoclonal gammopathy have been used, the MGUS is a better term because of the unknown nature and unpredictable out-

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ÖZET

Lenfoproliferatif hastalıkların ekarte edildiği 9 karaciğer sirozlu hastanın serumunda monoklonal gammopati tespit edildi. M-proteinin tipi 4 vakada IgG kappa, 3 vakada IgM lambda, 2 hastada ise IgA kappa idi. Sadece bir hastada Bence-Jones proteinürisi saptandı. Tüm hastalarda kemik iliğinde plazma hücreleri oranı %5'den azdı (% 1-3 arası). Serum B-2 mikroglobulin düzeyleri normal idi ve 4 hasta hariç tümünde serum immunoglobulinleri normal konsantrasyonda idi. 6-24 ay süre ile izlenen 4 hastada klinik ve laboratuvar bulguları stabil kaldı.

Anahtar Kelimeler: Karaciğer sirozu, Monoklonal gammopati

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come of this abnormality (2). The risk of developing lymphoproliferative disease has been reported to be very low but can not be excluded. MGUS may occur in collagenous and autoimmune diseases, chronic infections, carcinoma, immunodeficiency states and elderly people. In large series of MGUS, small number of patients who had monoclonal gammopathy and liver disease such as acute hepatitis or cirrhosis has been recited (2,3,4,5). The features of monoclonal gammopathy occurred in liver disease is not well known. In this study we present main features of monoclonal gammopathy detected in 9 patients with liver cirrhosis.

MATERIAL AND METHODS

The monoclonal gammopathy was detected by routinely performed serum protein electrophoresis in 9 (2%) of 510 patients with liver cirrhosis seen at the Gastroenterology department of İstanbul Medical Faculty between 1986-1991. The diagnosis of liver cirrhosis was confirmed by biopsy and/or peritoneoscopy in all cases. Serum protein electrophoresis was done by cellulose acetate technique. Serum IgG, IgA and IgM

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were quantitatively determined by radial immunodiffusion. Serum and urine immunoelectrophoresis were carried out using the anti-serums of IgG, IgM and IgA kappa and lambda light chains. Biochemical and serological tests, determination of serum beta-2 (B-2) microglobulin, bone marrow aspiration and bone X-rays were performed by standard methods.

RESULTS

Eight patients were male and one was female. Mean age was 58±12 ranging from 42 to 82. The cause of liver cirrhosis was hepatitis B virus in 3, hepatitis C virus in 1, alcohol in 1 and Wilson's disease in 1 patient. In 3 patients no etiological factor was identified and they were defined as cryptogenic cirrhosis. According to the Child classification 6 patients were Child B, 2 were Child A and 1 was Child C. All patients had splenomegally and 3 had hepatomegaly. No patients had peripheral lymphadenopathy. Two patients had hepatocellular carcinoma diagnosed by peritoneoscopy.

Renal functions were normal in all patients but 2 who had mild azotemia. Serum alkaline phosphatase and calcium levels were normal in all patients. Of 3 patients with high transaminases (greater than 3 times of upper limit of normal), in 2 hepatocellular carcinoma and in 1 spontaneous reactivation of hepatitis B were detected. Erythrocyte sedimentation rate was high in all patients, with mean 49±37 ranging from 25 to 145 mm/hour. All patients but 2 had varying degrees of anaemia, leucopenia and thrombocytopenia due to hypersplenism. Prothrombin time was prolonged greater than 3 seconds of control in 5 patients.

All patients had low serum albumin with normal or increased serum total protein concentration varying between 6.1-11.5 g/dl. Monoclonal gammopathy was always localised between beta and gamma bands of serum protein electrophoresis. All but 1 patients had M-protein less than 3 g/dl. Quantitative analysis of serum immunoglobulins revealed high IgG in 3, normal IgG in 1 and low IgG level in 1 patient. Immunoglobulin le-

vels ran parallel to serum gamma-globulin levels (Table 1).

Immunoelectrophoresis showed IgG kappa in 4, IgM lambda in 3 and IgA kappa light chains in 2 patients. Bence-Jones proteinuria was detected in only 1 patients who had IgM lambda light chain. In patients with hepatocellular carcinoma, light chains were IgM lambda and IgG kappa (Table 1). Serum B-2 microglobulin level was studied in 4 patients and found to be normal (between 1.2-1.7 mg/l). The number of plasma cells in bone marrow aspiration was normal as 1% in 6, 2% in 2 and 3% in 1 cases. No pathological lesion was detected in skull, pelvis and chest X-rays.

One patient died due to severe hepatic failure at the first admission to the hospital. In 4 patients followed by 6-24 months no significant changes developed in clinical and laboratory findings. The changes in the amount of M-protein stayed within 3% of the initial value. We do not have enough follow-up data about other 4 patients because they have not attended outpatient clinic.

DISCUSSION

The serum protein electrophoresis of patients with liver cirrhosis is characterized by hypoalbuminemia and polyclonal hyperglobulinemia. The hyperglobulinemia of liver cirrhosis is usually explained by the damaged function of Kupffer cells and the presence of porto-systemic collaterals which allow the wide variety of antigenic stimulants to enter systemic circulation and result in increased immunoglobulin production in reticuloendothelial system located in different parts of human body as a result of extensive antigenic stimulation (6). In addition, decreased inhibitor effect of suppressor T cells in liver cirrhosis may contribute increased antibody production by B lymphocytes (7). This abnormal immunologic response leads an substainal increase in the production of all immunoglobulins but mainly gamma-globulin. It has been proposed that this increased and long-term antigenic stimulation may cause monoclonal gammopathy in liver cirrhosis (7).

Table 1. Clinical and laboratory features of cirrhotic patients with monoclonal gammopathy.

No	Age-Sex	Child	Etiology	Ca mg/dl	Alk.P. BLU	Albumin g/dl	Gamma gl. g/dl	M-prot. g/dl	IgG mg/dl	IgA mg/dl	IgM mg/dl	B2 mik*'' mg/dl	M-Gammopathy
1	60-M	B	Alcohol	8.6	1.3	3.65	1.66	0.68	2240	430	176	1.5	IgG-kappa
2	42-M	B	Cryptogenic	8.8	2.6	3.34	3.49	0.25	3770	319	176	1.2	IgG-kappa
3	58-F	C	HBV	7.3	2.9	2.25	1.73	1.63	2440	634	339	1.3	IgG-kappa
4	45-M	A	Wilson	9.0	3.0	3.27	0.95	1.54					IgG-kappa
5*	55-M	B	HBV	7.8	2.8	3.0	4.1	2.8					**IgM-lambda
6	66-M	B	HCV	8.6	1.9	3.0	0.3	2.3	250	162	200	1.7	IgM-lambda
7	53-M	B	Cryptogenic	8.9	4.2	3.67	3.16	0.92	3770	515	109		IgM-lambda
8*	82-M	B	HBV	8.4	3.0	2.80	0.85	1.03					IgA-kappa
9	65-M	A	Caryptogenic	8.7	2.0	3.15	1.09	3.01	1470	305	103		IgA-kappa

* with hepatocellular carcinoma
with Bence-Jones proteinuria
Beta-2 microglobulin

Blade and et al (8) suggested that the development of multiple myeloma in a patient with primary biliary cirrhosis was secondary to increased and continuous antigenic stimulation.

MGUS is characterized by the serum M-protein less than 3 g/dl, plasma cells than 5% in bone marrow, normal renal functions and the absence of urinary M-protein, lytic bone lesions, hypercalcemia and very high (>100 mm/hour) erythrocyte sedimentation rate (1,9). In this series, all patients generally fit these criteria except 1 patients with borderline M-protein level (3.01 g/dl). Although M-protein of IgM and IgA is usually less than 2.5 g/dl (9), our patient with relatively high M-protein level has IgA kappa light chain. The high erythrocyte sedimentation rate detected in 2 patients (50 and 145 mm/hour) can be attributed to hepatocellular carcinoma complicating cirrhosis. Hypersplenism was responsible for anameia, leucopenia and thrombocytopenia. No patient had hypercalcemia. Mild azotemia seen in 2 patients was due to extensive use of diuretics and they were corrected by withdrawal of diuretics. In a large series of MGUS including 673 cases, IgG type M-protein was reported as the most frequent monoclonal gammopathy with decreasing frequency of IgA, IgM and IgD type M-protein (10). IgG type M-gammopathy was the more prevailing type of M-protein in our patients as well.

MGUS may be associated with reciprocal decrease in serum concentration of normal immunoglobulins in one third of patients, in particular, with M-protein level greater than 2 g/dl (11). One of our patients who had M-protein 2.3 g/dl showed low IgG level. Normal B-2 microglobulin level is one of the most important criteria in the discrimination of MGUS from malignant monoclonal gammopathy and its level runs parallel to the size of the tumour in multiple myeloma (12). It has been reported that Waldenstrom's macroglobulinemia and multiple myeloma are always associated with increased (>3 mg/l) serum B-2 microglobulin concentration (13). All patients had low B-2 microglobulin levels less than 2 mg/l in our series. Thymidine labelling index, immunotyping of peripheral blood lymphocytes and histochemical staining of plasma cells are the more sophisticated methods used to exclude the lymphoproliferative disorders in patients diagnosed having MGUS (14). Our patients had typical laboratory findings of MGUS and none of them had clinical features of lymphoproliferative disorders. There was no relationship between the etiology of cirrhosis and the monoclonal gammopathy.

Patients with MGUS require long-term follow-up to detect whether they develop lymphoproliferative disorders. Kyle et al (15) have reported that 22% of 241 patients with MGUS developed lymphoproliferative disorders such as multiple myeloma, macroglobulinemia, amyloidosis. They also detected that 3% of patients showed an important increase in M-protein level without any evidence of lymphoproliferative disorders. In

4 patients who were followed relatively short time (6-24 months) we did not find any change in the clinical and laboratory features. Since MGUS has an unpredictable course and since multiple myeloma may be associated with low M-protein level such as less than 3 g/dl, all cirrhotic patients with M-protein are needed a detailed investigation and long-term follow-up to recognize lymphoproliferative disorders.

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