American Journal of Hematology 60:140–142 (1999)

Myeloma Ascites—A Favorable Outcome With Cyclophosphamide Therapy

Dean Keren,[1] Lilian Schliamser,[2] Dina Atias,[2] Daniel Yeshurun,[1] and Eli Zuckerman[1]*

[1]Department of Internal Medicine ''A,'' Bnai-Zion Medical Center, Haifa, Israel
[2]Division of Hematology, Bnai-Zion Medical Center, Haifa, Israel

A 71-year-old woman with multiple myeloma (MM) in remission was admitted for evaluation of recent abdominal distension and was diagnosed as having massive myeloma ascites. The fluid was characterized by a total nucleated cell count of 6,600/mm^3 (67% plasma cells), with a plasma cell CD38+ phenotype. Chemical analysis of the fluid showed lactate dehydrogenase of 122 IU/L, total protein of 2.9 g/dL, albumin of 2.4 g/dL, diastase of 38 IU/dL, cholesterol of 46 mg/dL, and C-reactive protein of 3 g/dL. The serum-ascites albumin gradient (SAAG) was low (0.9). Electrophoresis of the ascitic fluid showed a monoclonal spike in the gamma region and immunoelectrophoresis confirmed the presence of lambda light chains similar to those seen in the urine. Further analysis of the ascitic fluid showed markedly elevated levels of β_2 microglobulin (11,161 μg/L) and interleukin-6 (146 pg/ml compared to serum level of 4.3 pg/ml). There was evidence of intraabdominal masses that completely resolved with continuous high-dose cyclophosphamide (750 mg/m^2/day for four days) followed by clinical improvement and disappearance of the ascites. We stress the value of complete fluid characterization and intensive chemotherapy to achieve a favorable outcome. Am J Hematol. 60:140–142, 1999.

Key words: myeloma ascites; multiple myeloma; cyclophosphamide; ascitic fluid; interleukin 6; beta-2 microglobulin

INTRODUCTION

Ascites formation is a rare complication of multiple myeloma (MM). It is usually associated with massive liver infiltration by malignant plasma cells, leading to portal hypertension [1]. Less frequently, myeloma ascites is caused by peritoneal involvement by myeloma cells which is an exceedingly rare complication of extramedullary MM [2–8]. Infiltration of the peritoneum by malignant plasma cells and ascites formation carries a grave prognosis in the vast majority of cases and is resistant to chemotherapy [2–5,9–12].

We report a case of myelomatous ascites in which the ascitic fluid was fully characterized and intensive chemotherapy led to complete resolution of the ascites.

CASE REPORT

A 71-year-old Caucasian female presented to our ward with complaints of abdominal distention and tenderness three weeks prior to admission. Diagnosis of light chain myeloma was made in February 1996 when she presented with compression fractures of the lumbar spine, lytic lesions in the skull, low serum immunoglobulin levels, and massive proteinuria of monoclonal free lambda light chains (3.1 g/24 hr), but with no extraosseous involvement. Fifty percent of the marrow was infiltrated with myeloma cells and the pretreatment β_2 microglobulin level was 4,234 μg/L (normal <2,750 μg/L). In March 1996, she underwent radiotherapy to the lumbar spine and received six courses of VAD (vincristine, adriamycine, and dexamethasone) over a period of six months, bringing her into a plateau phase. The β_2 microglobulin decreased to 2,519 μg/L with no detectable free light chains in the urine. Maintenance treatment with interferon, 3 million units three times a week, was then initiated. In February 1997 she underwent another course of radiotherapy to the pelvis, skull, and chest for symptomatic localized plasmacytomas. Thirteen months after the initial diagnosis of MM, she presented with massive

*Correspondence to: Eli Zuckerman, M.D., Department of Internal Medicine ''A,'' Bnai-Zion Medical Center, 47 Golomb St., Haifa, 31048 Israel. E-mail: drkeren@isdn.net.il

Received for publication 27 March 1998; Accepted 2 September 1998

ascites. Serum albumin level was 3.3 g/dL, globulin was 1.9 g/dL, lactate dehydrogenase (LDH) was 201 IU/L and calcium was 9.4 mg/dL. Renal function, serum electrolytes, and liver tests were within normal limits. A monoclonal lambda light chains spike reappeared in the urine and was associated with massive proteinuria of 3.6 g/day and a three-fold increase of serum β_2 microglobulin level (7,878 μg/L), while serum protein electrophoresis was within normal limits. Serological markers for hepatitis B and hepatitis C viruses were absent. Ascites was massive and necessitated recurrent paracentesis which revealed a straw-colored and cloudy fluid. Stains for acid fast bacilli and cultures for mycobacteria and fungi were all negative. Total nucleated cell count was 6,600/mm^3 of which 67% were plasma cells. The majority of these cells were atypical while multinucleation was common. Flow cytometry showed that about 45% of the cells in the peritoneal fluid had a phenotype of plasma cells CD38+, of which intracellular CD138/lambda was strongly positive in 88% of the cells. Chemical analysis of the fluid showed LDH of 122 IU/L, total protein of 2.9 g/dL, albumin of 2.4 g/dL, diastase of 38 IU/dL, cholesterol of 46 mg/dL, and C-reactive protein of 3 g/dL. The serum-ascites albumin gradient (SAAG) was low (0.9). Electrophoresis and immunoelectrophoresis of the ascitic fluid confirmed the presence of lambda light chains spike similar to those seen in the urine. Further analysis of the ascitic fluid showed markedly elevated levels of β_2 microglobulin (11,161 μg/L) and interleukin (IL)-6 (146 pg/ml compared with serum level of 4.3 pg/ml). Additional imaging studies revealed normal isotope scans of the liver and spleen. Doppler ultrasonography of the vena cava, hepatic veins, and portal veins showed no evidence of obstruction. Computerized tomography (CT) of the chest, abdomen, and pelvic area showed a large amount of ascites, a 45 mm mass medial to the right kidney, and another 15 mm mass posterior to the stomach. Gallium scan was unremarkable. Chemotherapy was initiated and consisted of high-dose cyclophosphamide (750 mg/m^2/day for four days). Two weeks after the first chemotherapy course, the amount of ascitic fluid substantially decreased. She has received four more courses of high-dose cyclophosphamide, inducing the disappearance of the previously described abdominal masses and complete resolution of ascites as demonstrated by follow-up ultrasonography and abdominal CT examination. While reporting the case, eight months after the initial presentation with massive ascites, she has no ascitic fluid, proteinuria decreased to 0.12 g/day, and there are no detectable light chains in the urine.

DISCUSSION

The present case represents an extremely rare presentation of relapse of MM and an unusual cause of ascites. Interestingly, the formation of ascites in our patient reflected a relapse of MM at the extramedullary site. The diagnosis of myeloma ascites was made based on the presence of numerous atypical plasma cells in the ascitic fluid along with a low SAAG and a typical immunoelectrophoresis demonstrating a monoclonal spike of lambda light chains in the ascitic fluid.

Ascites formation in a myeloma patient is usually associated with extensive liver infiltration with plasma cells, but may be secondary to infectious peritonitis or myelomatous peritoneal infiltration [1–5]. The possibility that postsinusoidal portal hypertension might be a cause of ascites in myeloma patients was suggested by postmortem studies that showed that liver infiltration with myeloma cells occurred in 40% of myeloma patients, while 10% of those patients had extensive myelomatous liver infiltration and ascites [1]. Other possible etiologies of ascites in MM patients are systemic amyloidosis, tuberculous peritonitis, hemangioendothelial sarcoma, plasma cell sarcoma, and spontaneous splenic rupture [6–8,13,14]. To the best of our knowledge, this is the first case in which the myelomatous peritoneal fluid was carefully characterized. The LDH ascites-to-serum ratio was 0.6 (122 IU/L/201IU/L) which indicated an exudative form of ascites. The ascitic fluid was characterized by a low SAAG (the difference between serum and ascitic fluid albumin concentration) which indicates peritoneal disease, while high SAAG ascites (>1.1) reflects portal hypertensive ascites regardless of the protein concentration in the ascitic fluid, which may be high [15]. The differential diagnosis of a low SAAG ascites includes malignant, infectious, or inflammatory peritonitis [12]. The low SAAG, which was not previously documented in any of the cases of myeloma ascites, combined with the absence of massive myelomatous infiltration of the liver, and the markedly increased number of plasma cells in the ascitic fluid also supports myelomatous involvment of the peritoneum [1,3–5]. Greer et al. concluded that if ascitic fluid in a myeloma patient contains more than 800 cells/mm, it is likely caused by peritoneal implantation of the tumor [3,16]. Of interest is the extremely high level of IL-6 in the ascitic fluid: 146 pg/ml, compared with serum level of 4.3 pg/ml. This high ascites-to-serum ratios of IL-6 indicates that IL-6 is produced in high amounts in the peritoneal cavity and supports the diagnosis of myelomatous peritoneal involvement [17–19]. Tatsumi et al. described elevated levels of IL-6 in myelomatous ascitic fluid and suggested that IL-6 is a potent growth factor of myeloma cells in the ascites that may accelerate growth of myeloma [9]. The ascitic fluid in the present case was also characterized by elevated β_2 microglobulin (11,161 μg/L). This finding is consistent with the diagnosis of malignant ascites as reported by Kin et al. [20]. They postulated that the high serum and ascitic level of β_2 microglobulin could be

attributed to its cytokine-mediated hyperproduction by tumor cells or by activated infiltrated cells.

Importantly, as opposed to previously reported cases, our case showed a favorable response to intensive systemic chemotherapy with high-dose intravenous cyclophosphamide. Previous reports showed a poor response to treatment of myeloma ascites, when using intraperitoneal instillation of thiotepa, nitrogen mustard, and radioactive $CR^{32}PO_4$ [3,4,5,12], irradiation of the whole abdomen, or even systemic chemotherapy with VAD [19]. In several other cases of refractory myeloma ascites or pleural effusion, the only favorable response to treatment was achieved when systemic cyclophosphamide was administered [16,19,20]. The vast majority of the previously reported cases of myeloma ascites had extremely poor prognosis as reflected by their very short survival of less than five months after the diagnosis of myeloma ascites [2–5,7,10–12].

All the parameters described—the elevated plasma cell count in the ascitic fluid, the low SAAG, high IL-6, increased level of ascitic β_2 microglobulin, and evidence of intraabdominal masses upon the patient's admission, which resolved under additional chemotherapy—lead us to the conclusion of a peritoneal involvement of her myelomatous process. This case and the review of the literature emphasize the grave prognosis of this entity and the necessity of careful characterization. It also stresses the value of intensive chemotherapy such as systemic high-dose cyclophosphamide in achieving a better outcome.

REFERENCES

1. Thomas FB, Clausen KP, Greenberger NJ. Liver disease in multiple myeloma. Arch Intern Med 1973;132:195–202.
2. Bank H, Liberman SI. Sister Joseph's nodule and malignant ascites in multiple myeloma. N Engl J Med 1971;284:676–677.
3. Lucas RU, Schneider JR, Axelrod AR. Multiple myeloma with massive ascites—Report of a case. Harp Hosp Bull 1968;26:216–220.
4. Higby DJ, Ohnuma T. Plasmacytoma cell ascites. NY State J Med 1975;75:1074–1076.
5. Poth JL, George RP. Hemorrhagic ascites: An unusual complication of multiple myeloma. Calif Med 1971;115:61–64.
6. Gomes D, Oliverira JJ, Odette M, De Almeida OM, Carneiro Demoura M, Guerra L, Ducla-Soares A. Multiple myeloma with massive plasma cell ascites [abstract]. Presented at the sixth meeting of the International Society of Hematology, European and African Division: Hellenic Society of Hematology; 1981.
7. Koeffler HP, Cline MJ. Multiple myeloma presenting as ascites. West J Med 1977;127:249–250.
8. Gravanis MD, Majmudar BN. Clinicopathologic conference: A case of multiple myeloma followed up for 15 years. South Med J 1976;69: 233–238.
9. Tatsumi T, Okada M, Yoneda Y, Maki K, Ura Y, Sawada K, Hino R, Goto H, Fujita N, Shimazaki C. Multiple myeloma with massive asictes fluid-immunophenotypic analysis of myeloma cell and its IL-6 independent growth. Rinsho Ketsueki 1994;35(12):1361–1365.
10. Durant JR, Barry WE, Learner N. The changing face of myeloma. Lancet 1966;1:119–121.
11. Matsumoto A, Nagata K, Hamaguchi H, Taki K. Solitary bone plasmacytoma terminally developed myeloma with multiple extramedullary lesions and myelomatous pleural effusion and ascites. Int J Hematol 1993;59(1):59–65.
12. Zuckerman E, Kanel G, Chung HA, Kahn J, Gottesman B, Korula J. Low albumin gradient ascites complicating severe pseudomembranous colitis. Gastroenterology 1997;112:991–994.
13. Fujii H, Seki S, Syama Y, Shimizu T, Kano T, Yasuda N. A case of solitary myeloma (BJ-lambda) showing marked morphological changes. Gan No Rinsho 1983;29(4):A–A22.
14. Stephens PJT, Hudson P. Spontaneous rupture of the spleen on plasma cell leukemia. Can Med Assoc J 1969;100:31–34.
15. Runyon BA. Ascites. In: Schiff L, Schiff ER, editors. Diseases of the liver. Volume 2. 7th ed. Philadelphia: J.B.Lippincott Company; 1993. p 990–1015.
16. Greer JP, Pinson RD, Russell WG, Keith TA, Collins RD, Graber SE. Malignant plasmacytic ascites—A report of two cases and a review of the literature. Cancer 1985;56:2001–2004.
17. Andus T, Gross V, Holstege A, Weber M, Ott M, Gerok W, Scholmerich J. Evidence for the production of high amount of IL-6 in the peritoneal cavity of patients with ascites. J Hepatol 1992;15:378–381.
18. Bac DJ, Pruimboom WM, Mulder PG, Zijlstra FJ, Wison JH. High IL-6 production within the peritoneal cavity in decompensated cirrhosis and malignancy-related ascites. Liver 1995;15(5):265–270.
19. Ohmoto A, Kohno M, Yasukawa K, Matsuyama R. Massive ascites as an initial sign, plasmacytoma of the cervical spine, and hyperammonemic consciousness disturbance in a patient with biclonal type multiple myeloma. Rinsho Ketsueki 1996;37(4):346–351.
20. Kin K, Saurabayashi I, Kawai T. Beta2-microglobulin levels or serum and ascites in malignant diseases. Gann 1977;68(4):427–434.
21. Shoenfeld Y, Pick Al, Weinberger A, Ben-Bassat M, Pinkhas J. Pleural effusion-presenting sign in multiple myeloma. Respiration 1978;36(3):160–164.-