IgG Lambda Myeloma Presenting as Plasmacytic Ascites: Case Report and Review of Literature

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Received: 20 July 2014 / Accepted: 20 August 2014 / Published online: 3 September 2014
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Abstract Multiple myeloma is a neoplastic disease of plasma cells accounting for 13 % of haematological malignancies and 2 % of all malignancies worldwide. Ascites may develop very rarely during the course of disease in multiple myeloma. We report the case of a 78 years old male with IgG lambda multiple myeloma who initially presented with plasmacytic ascites. An exhaustive review of world literature reveals 65 cases of ascites to have been reported in myeloma over a span of 62 years (1952 till date), usually developing in the course of treatment. This is the 7th case of plasmacytic ascites to have been diagnosed at initial presentation. We review the clinical features, diagnosis, prognostic significance and treatment of such cases.

Keywords Multiple myeloma · Ascites · Plasmacytic ascites · IgG lambda

Introduction

Multiple myeloma accounts for approximately 2 % of all malignancies and 13 % of haematological malignancies worldwide. Common clinical symptoms are bone pain, weakness, infections, hypercalcemia, and pallor [1, 2].

Ascites is an infrequent complication of multiple myeloma and usually develops during course of the disease due to hepatic involvement, peritonitis, peritoneal infiltration or amyloidosis involving kidney. IgG and IgA myelomas are more commonly associated with ascites. We report here a case of IgG-lambda multiple myeloma presenting initially with plasmacytic ascites; along with a review of literature of published cases till date.

Case Report

A 78-year-old male presented to the hospital with complaints of abdominal distention and pain of 3 months duration. There was no history of weakness, bone pain, weight loss or anorexia. Physical examination showed mild pallor without jaundice, moderate ascites and mild pedal edema. There was no palpable lymphadenopathy or hepatosplenomegaly. Complete hemogram showed a Hb of 80 gm/L, normal total and differential leucocyte counts (WBC $7.5 \times 10^9/l$ with 52 % neutrophils, 40 % lymphocytes, 6 % monocytes and 2 % eosinophils) and a normal platelet count of $155 \times 10^9/l$. Erythrocyte sedimentation rate was increased, at 140 mm/1st hour.

Serum sodium (136 mmol/L), potassium (4.8 mmol/L), urea (25.4 mg/dL) and creatinine (1.46 mg/dL) levels were normal. Liver function tests were normal with a total serum bilirubin of 0.22 mg/dL ($N < 1.2$ mg/dL), AST 27 IU/l ($N < 35$ U/L), ALT 16 IU/l ($N < 41$ U/L), GGT 13 IU/l ($N < 55$ U/L) and alkaline phosphatase 46 IU/l ($N < 119$ U/L). Total protein was high at 9.4 g/dl with increased globulin (3.07 g/dl albumin, A/G ratio of 0.46).

Computerized tomographic (CT) scan of the abdomen revealed moderate ascites, mesenteric and omental thickening, multiple peritoneal nodules, mesenteric and

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retroperitoneal lymphadenopathy and evidence of minor renal cortical disease (Fig. 1a). Abdominal paracentesis was done and 100 ml of yellowish fluid aspirated. Laboratory evaluation of the ascitic fluid showed a total protein content of 7.75 g/dL including 2.29 g/dL albumin, and moderately increased adenosine deaminase (ADA) levels at 36.8 U/L ($N < 24$ U/L). Cell count was 4,000/mm³ and 480 erythrocytes/mm³.

Smears prepared from centrifuged deposits were stained by a modified Wright-Giemsa method. The fluid was centrifuged and air dried smears prepared from the deposits. Smears were highly cellular and showed a discohesive population of plasma cells having eccentric nuclei, “cart-wheel” chromatin, perinuclear hof, and dense basophilic cytoplasm. Bi- and multi-nucleate forms were also seen. A differential cell count showed 79 % plasma cells, 12 %

lymphocytes, 5 % macrophages, 3 % mesothelial cells, and 1 % neutrophils. Routine microbiological culture of the ascitic fluid was negative for common bacteria and fungi.

Additionally, serum protein electrophoresis was done at alkaline pH and showed a sharp and distinct band in the beta2 region of 4.28 g/dL. Serum immunofixation electrophoresis at alkaline pH showed beta corresponding bands in IgG heavy chain and lambda light chain regions. Quantification analysis showed highly elevated levels of IgG at 4,977.92 mg/dL (N 700–1,600 mg/dL). Roentgenographic examination showed scattered radiolucent lesions in the parietal bones of skull and in the dorsal vertebrae. Bone marrow aspiration and trephine biopsy was done and showed an increase in plasma cells to 22 % of the marrow nucleated cell population (Fig. 1b). 24 h urinary excretion of protein was within normal limits, and urinary protein

Fig. 1. a CT (Computed tomography) scans of abdomen showing mesenteric thickening and peritoneal nodules b Bone marrow aspirate smears with increased plasma cells, and bi nucleate forms (modified Wright-Giemsa stain, $\times 400$) c Numerous plasma cells in cell block

preparation (modified Wright-Giemsa stain, $\times 400$) d CD 138 positivity in plasma cells, cell block preparation (Immunoperoxidase, $\times 400$)

immunofixation electrophoresis did not reveal any monoclonal proteins. Serum beta 2-microglobulin level was 6.2 mg/L. Immunohistochemistry done on cell-block prepared from ascitic fluid deposits showed that the cells were CD138 positive (Fig. 1c, d). CT guided biopsy of retroperitoneal lymph nodes and peritoneal nodules showed infiltration by plasma cells.

The patient was diagnosed as a case of multiple myeloma, IgG lambda, International staging system (ISS) stage III.

Discussion

The world wide incidence of myeloma is 86,000 cases annually. Mortality rates in multiple myeloma are high, with a median survival of 50–55 months, and 63,000 deaths being reported worldwide each year. The higher incidence in more developed countries may result from the combination of a longer life expectancy, more frequent medical surveillance and heightened awareness of the disease. Estimated incidence in India varies from 0.3 to 1.9 per 1,00,000 for men and 0.4 to 1.3 per 1,00,000 for women. The age incidence in India is nearly a decade less than that in the USA, at 55 years [2–5].

Patients usually present with complaints of bone pains, anaemia, renal failure or soft tissue masses. Further evaluation often reveals renal failure, hypercalcemia, hyperuricemia and signs of nerve compression or amyloidosis [5].

Ascites rarely develops in multiple myeloma, and may be due to hepatic infiltration, heart failure, renal damage, portal hypertension due to hepatic amyloidosis, infectious peritonitis (including tuberculosis) or peritoneal infiltration with tumour [6]. In a review of myeloma cases with extramedullary manifestations, only 3 of 182 cases showed peritoneal involvement [7]. A review of 64 necropsies of patients with multiple myeloma revealed exudative ascites in nine cases, but with no evidence of peritoneal infiltration [8]. No peritoneal involvement was detected in another series of 32 autopsies, while one case was detected in a series of 30 autopsies limited to patients with extraosseous myeloma [9, 10].

Histological evidence of hepatic infiltration has been found in up to 53 % of patients with multiple myeloma. This can be either nodular or diffuse sinusoidal infiltration, and lead to portal hypertension [8, 9]. Secondary ascites arising due to hepatic involvement, renal damage or cardiac failure in myeloma patients is characterized by serous effusion with a cell count of 30–120 cells/mm³. This needs to be differentiated from malignant plasmacytic ascites with plasma cells present in ascitic fluid, and a cell count of 800–9,000 cells/mm³. Plasmacytic ascites is strongly

associated with peritoneal tumour implantation and liver involvement is minimal or absent in the majority of cases [6, 11, 12]. The cytological appearance of plasma cells in the ascitic fluid is often highly atypical, with numerous large, bizarre and immature cells, and lack of cohesion. This can lead to diagnostic confusion with reactive mesothelial cells, transformed lymphocytes, or metastatic carcinoma cells [13]. Immunocytochemistry, flow cytometry, immunofluorescence, or electron microscopy can be used to identify the plasma cells. In the present case, total cell count was 4,000/mm³, with 79 % plasma cells which were CD138 positive.

ADA levels can be elevated in plasmacytic ascites, and this has been attributed to peritoneal infiltration by myeloma [14]. Increased levels of IL-6 (Interleukin-6) in ascitic fluid have been reported in cases of plasmacytic ascites, with myeloma cells showing IL-6 dependent growth, and growth inhibition by anti IL-6 Ab (antibody) or anti IL-6 receptor Ab, in vitro. An autocrine mechanism involving IL-6 has been postulated in the rapid proliferation of myeloma cells and aggressive course of plasmacytic ascites [15, 16]. High levels of β 2 microglobulin in ascitic fluid have also been reported, probably a result of cytokine overproduction in myeloma [17, 18].

In a comprehensive review of world literature, we have found 65 cases of ascites in myeloma patients. Plasmacytic ascites was diagnosed in 27 cases, and was a presenting symptom in only seven cases.

Based on the 49 cases where data was available, a male:female patient ratio of 1:23 was found (27 males, 22 females). The average age at diagnosis for the patients was 60.6 years; 60.2 years for males, and 61 years for females. There was evidence of peritoneal involvement in 34 cases out of 41 where data was available (82.9 %). The presence of a clonal immunoglobulin had been characterized in 44 cases, and IgG was found in 50 % cases, including one case of biclonal expression of IgG with IgA [19]. IgA was found in 34 % cases (15 cases) including one case of biclonal expression with IgD [16]. Three cases of clonal IgD [14, 20], two cases of monoclonal light chain production [21, 22], one case of clonal IgE production [23], and one nonsecretory myeloma was reported.

Pleural effusion can accompany ascites, and 13 such cases have been reported. Five cases of extramedullary plasmacytomas with ascites and no skeletal involvement have been reported; while in four cases, plasmacytoma was associated with development of multiple myeloma. Systemic amyloidosis has been reported in three cases, and plasma cell leukemia has been reported in two cases only (Table 1).

The epidemiological profile of patients with myelomatous ascites is comparable to that of myeloma patients without ascites. In a large series of 1,027 myeloma patients, the median age of diagnosis was 66 years and

Table 1 Ascites associated with plasma cell dyscrasia – 65 reported cases (1952–2014)

Reference (No. of cases)	Ascites at ^c presentation	Plasma cells in ascitic fluid	Age, Sex	Immunoglobulin	Skeletal lesions	Peritoneal involvement	Plasma cell dyscrasia
Hayes et al. ^a [7] (3)	NA	–	47 F(2), NA (1)	Ig-G (1), NA (2)	Yes (1), NA (2)	Yes (2), NA (1)	MM (3)
Michelson et al. [28] (1)	Yes	–	NA	NA	NA	NA	MM
Durant et al. ^a [42] (1)	NA	–	48 M	M Band	NA	Yes	MM
Lucas et al. ^a [43] (1)	No	–	51 F	M Band	Yes	Yes	MM
Line et al. ^a [44] (1)	No	Yes	46 M	M Band	No	Yes	Plasmacytoma
Bank et al. ^a [45] (1)	NA	–	63 M	IgA	Yes	Yes	MM
Poth et al. ^a [11] (1)	No	Yes	45 F	IgG-k	Yes	Yes	MM
Thomas et al. [8] (7)	No	–	NA (7)	NA (7)	Yes	No (7) ^a	MM (7)
Okada et al. [29] (1)	No	–	NA	NA	NA	NA	MM
Higby et al. a [12] (1)	No	–	76 M	IgA-k	No	Yes	Plasmacytoma
Gravanis et al. ^b [46] (1)	No	–	55 M	IgG	Yes	Yes	MM
Koeffler et al. ^a [47] (1)	Yes	Yes^d	57 F	IgA-L	No	Yes	MM
Faux et al. ^b [48] (1)	Yes	–	83 M	IgA-L	No	NA	MM
Gomes et al. ^a [49] (1)	Yes	Yes^d	69 F	IgG-k	Yes	Yes	MM
Renau-Piqueras et al. [30] (1)	No	Yes	NA	NA	NA	NA	MM
Fujii et al. [21] (1)	No	–	49 M	BJ-Lambda	No	Yes	Plasmacytoma
Estrov et al. ^a [50] (1)	Yes	–	60 F	IgA	NA	NA	MM
Morgan et al. ^b [51] (1)	No	–	51 M	IgA-k	Yes	Yes	MM
Greer et al. ^a [13] (2)	No(2)	Yes (2)	57 M, 47 F	IgG-k, Ig-G	Yes (2)	Yes (2)	MM (2)
Karp et al. ^a [6] (1)	Yes	Yes^d	70 F	IgG	No	Yes	MM
Görg et al. [26] (1)	No	Yes	47 M	IgA-k	No	Yes	MM
Vinti et al. ^b [52] (1)	NA	–	59 M	IgA-L	Yes	Yes	MM
Gardais et al. ^b [53] (1)	NA	–	74 F	IgD	Yes	Yes	MM
Sasser et al. ^b [54] (2)	NA	Yes (2)	82 F, 62 M	IgG-k, Nonsecretory	NA, No	Yes (2)	MM (2)
Fujii et al. [31] (1)	NA	–	NA	NA	NA (probable)	NA	MM
Matsumoto et al. [32] (1)	Yes	–	72 M	IgG-K	Yes	No	MM
Khoddami et al. ^b [55] (1)	No	Yes	68 F	IgG	Yes	NA	MM
Jackson et al. ^b [56] (1)	NA	–	63 F	IgG	No	Yes	Plasmacytoma
Matsumoto et al. ^b [57] (1)	No	–	51 F	IgG-K	Yes	Yes	MM Plasmacytoma
Kumar et al. [33] (2)	No	Yes (2)	Age-NA, M (2)	NA (monoclonal)	Yes (1), No (1)	NA	MM
Tatsumi et al. ^b [15] (1)	No	Yes	75 F	IgG-L	Yes	Yes	MM, Plasmacytoma
Ohmoto et al. ^b [16] (1)	Yes	–	69 M	IgA-L, IgD-k (biclinal)	Yes	No	MM
Wahid et al. ^b [58] (1)	NA	–	60 M	IgG-K	No	Yes	MM
Shimizu et al. ^b [34] (1)	Yes	Yes^d	80 F	IgA-L	No	Yes	MM
Alegre et al. ^b [25] (1)	No	Yes	51 F	IgG-K	No	No	MM

Table 1 continued

Reference (No. of cases)	Ascites at ^c presentation	Plasma cells in ascitic fluid	Age, Sex	Immunoglobulin	Skeletal lesions	Peritoneal involvement	Plasma cell dyscrasia
Keren et al. ^b [17] (1)	No	Yes	71 F	IgG-L	Yes	Yes	MM
Song et al. [27] (1)	Yes	–	76 M	IgA	No	Yes	MM
Kawanishi et al. ^b [59] (1)	Yes	–	NA	NA	NA	NA	MM
Singh et al. ^b [60] (1)	NA	–	45 M	IgG-L	Yes	No	MM
Inoue et al. ^b [61] (1)	No	Yes	51 F	IgG-L	No	Yes	MM
d'Assignies et al. [19] (1)	Yes	–	68 M	IgA, IgG-L	No	No	MM
Attwell et al. [35] (1)	No	–	57 F	IgA	No	Yes	MM
Shi et al. [36] (1)	Yes	–	NA	NA	NA	NA	MM
Young et al. [18] (1)	No	Yes	50 F	IgA-k	Yes	Yes	MM
Karanth et al. [37] (1)	Yes	Yes^d	50 M	IgA-k	No	Yes	Plasmacytoma
Yokoyama et al. [14] (1)	No	Yes	58 M	IgD-L	Yes	No	MM
Stoos-Veic et al. [38] (1)	NA	Yes	NA	NA	NA	NA	MM
Alacacioglu et al. [39] (1)	Yes	Yes^d	NA	IgG	NA	NA	MM
Ueda et al. [40] (1)	No	–	76 F	IgA-L	NA	No	MM, Plasmacytoma
Hagihara et al. [23] (1)	No	–	69 M	IgE-L	Yes	No	MM
Mahto et al. [22] (1)	Yes	–	38 M	Light chains	Yes	No	MM (LCDD)
Sekiguchi et al. [20] (1)	No	Yes	70 M	IgD-l, BJP (L)	NA	No	MM, Plasmacytoma
Mettler et al. [41] (1)	No	Yes	55 M	IgG-k, k light chains	Yes	Yes	MM
Current Report (1)	Yes	Yes^d	78 M	IgG-L	Yes	Yes	MM

A bold font had been added to highlight those cases in the review which had similar presentations to the case being discussed in Table 1. The bold number in brackets in the 1st column denotes the number of cases in each report

NA Data not available

^a Adapted from Karp et al. [6]

^b Adapted from Young et al. [18]

^c Ascites as a presenting symptom prior to diagnosis (17 cases)

^d Plasmacytic ascites diagnosed on initial presentation (7 cases)

Table 2 Review of treatment protocols used in myelomatous ascites

Reference	Therapy (after development of ascites), and clinical response to treatment(reduction in ascites); as CR: Complete response, PR: Partial response, and NR: No response	Age & Sex	Survival (in months) from time of	
			Diagnosis	Ascites development
Hayes et al. ^a [7]	Cyclophosphamide: NR, Intraperitoneal thiotepa: NR	47 F	5	2
Durant et al. ^a [42]	Steroids and androgens: NR, Melphalan:NR, Intraperitoneal thiotepa: NR, Cyclophosphamide: PR	48 M	NA	NA
Lucas et al. ^a [43]	Melphalan: PR, Intraperitoneal mustine: NR	51 F	3.5	1.5
Line et al. ^a [44]	Abdominal radiotherapy: NR	46 M	27	1
Poth et al. ^a [11]	Melphalan and prednisolone: NR, Intraperitoneal thiotepa: NR, Intraperitoneal radioactive CrP ³² O ₄ : NR	45 F	25	2
Higby et al. ^a [12]	Abdominal radiotherapy: CR	76 M	11	5
Gravanis et al. ^a [46]	Continuing cyclophosphamide regimen: NR	55 M	NA	NA
Gomes et al. ^a [49]	Plasmapheresis, melphalan and prednisolone: NR	69 F	1	1
Estrov et al. ^a [50]	Plasmapheresis: PR; Melphalan, prednisolone and cyclophosphamide: CR	60 F	30 (surviving)	30 (surviving)
Fujii et al. [21]	Plasmacytoma treated with chemotherapy & radiation: NR for ascites	49 M	60	3
Greer et al. ^a [13]	Melphalan and prednisolone: NR, Abdominal radiotherapy: NR	57 M	6	1
Karp et al. ^a [10]	Melphalan and prednisolone: NR, Denver shunt: NR	70 F	1.5	1.5
Görg et al. [26]	Initial VCMP regimen, I.v. Etoposide + Intermittent local Methotrexate + VAD regimen: PR (pleural effusion), PR(ascites)	47 M	60 (surviving)	48 (surviving)
Tatsumi et al. [15]	MCNU + MP therapy for myeloma: PR VAD regimen for ascites: NR	75 F	16	1
Ohmoto et al. [16]	Radiation therapy (bony lesion), MP therapy, Interferon- α , VAD therapy Intraperitoneal cyclophosphamide infusion: NR for ascites	69 M	NA	NA
Alegre et al. [25]	VAD regimen: CR for ascites High dose melphalan, busulfan conditioning + PBSCT: CR for myeloma. Maintenance – s.c. α 2b interferon	51 F	110 (surviving)	14 (surviving)
Keren et al. [17]	High-dose cyclophosphamide: CR of ascites	71 F	NA	NA
Shimizu et al. [34]	Melphalan + Prednisolone: PR of ascites	80 F	NA	NA
Song et al. [27]	Plasmapheresis, VAD regimen: CR of ascites	76 M	NA	NA
Young et al. [18]	Initial VAD regimen: CR of myeloma, followed by allogenic BMT Cyclophosphamide, Prednisolone for relapse: NR Palliation – Thalidomide	50 F	<36	<0.5
Hagihara et al. [23]	Melphalan + Prednisolone: PR Bortezomib, Dexamethasone: NR, Thalidomide: NR	69 M	30	<6
Mettler et al. [41]	Radiotherapy, Thalidomide, Dexamethasone: CR of myeloma, followed by autologous PBSCT For recurrent Plasmacytoma – Lenalidomide, Bortezomib, Dexamethasone: CR	55 M	NA	NA
Sekiguchi et al. [20]	MCNU-VMP regimen for myeloma: very good PR, maintained on MP Low dose bortezomib for ascites: CR Relapsed ascites— Low dose bortezomib: NR, High dose dexamethasone, VAD(2 courses), VCAP(1 course): NR	70 M	29	5

Table 2 continued

Reference	Therapy (after development of ascites), and clinical response to treatment(reduction in ascites); as CR: Complete response, PR: Partial response, and NR: No response	Age & Sex	Survival (in months) from time of	
			Diagnosis	Ascites development
Current Report, 2014	Bortezomib, Cyclophosphamide,Dexamethasone, Liposomal doxorubicin: very good PR	78 M	3 (surviving)	3 (surviving)

(Surviving) implies patient surviving till the time of case report

MP melphalan, prednisone, *VCMP* vincristine, cyclophosphamide, melphalan, and prednisone, *MCNU* ranimustine, *VMP* vindesine sulfate, melphalan, prednisolone, *VAD* vincristine/vinblastine, adriamycin(doxorubicin), dexamethasone, *VCAP* vincristine, cyclophosphamide, adriamycin(doxorubicin), prednisolone, *PBSCT* Peripheral blood stem cell transplantation, *BMT* Bone marrow transplantation

^a Adapted from Karp et al. 1987 [6]

59 % were males. A monoclonal protein was found in 93 % patients, majority of cases showing clonal IgG production (52 %), followed by clonal IgA (21 %) [24]. Ascites in myeloma presented at an earlier age on average, but the sex distribution and predominance of IgG is similar.

Myeloma without ascites has a median survival of 33 months [24]. Current management of myeloma is based on chemotherapy, and autologous peripheral blood stem cell transplantation in suitable cases [3, 5, 24].

Plasmacytic ascites may reflect the progression of disease to a more aggressive stage, or may be evidence of increased tumour burden or extensive extramedullary spread. Ascites carries a dismal prognosis, with reported cases indicating a median survival of 1.5–2 months from development of ascites. Only four reported cases have survived more than 12 months [25, 26].

The documented therapeutic protocols attempted in myelomatous ascites have been summarized in Table 2. Poor response to conventional chemotherapy is seen in most cases. Radiotherapy, plasmapheresis, intraperitoneal and systemic chemotherapy, as well as stem cell transplantation have been attempted with poor results in most cases. Newer novel agents like bortezomib have also been tried, with varying results. The current case was managed with bortezomib, cyclophosphamide, dexamethasone, and liposomal doxorubicin. After 1st cycle of chemotherapy, there was significant reduction in ascites, and symptomatic improvement. The patient remains under treatment and observation.

In conclusion, ascites can occasionally develop in multiple myeloma and is a poor prognostic feature. Undiagnosed multiple myeloma presenting with ascites is extremely rare, and in such cases, prompt fluid characterization and aggressive chemotherapy is indicated to achieve a better outcome.

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