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【 CASE REPORT 】

Nonmyelomatous Ascites Resulting from the Increased Secretion of Vascular Endothelial Growth Factor in Multiple Myeloma

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Abstract:
Ascites is a rare complication of multiple myeloma (MM); in most cases, the direct invasion of myeloma cells to the peritoneal cavity has been assumed to be the etiology because the effusion is usually exudative and contains a high proportion of myeloma cells. We herein report a case of MM with massive ascites containing only a small amount of myeloma cells. Instead, high levels of serum and ascitic vascular endothelial growth factor were detected. This was suggested to be a potential mechanism underlying the development of ascites.

Key words: multiple myeloma (MM), vascular endothelial growth factor (VEGF), pleural effusion, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS) syndrome

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Introduction

Ascites is a rare complication of multiple myeloma (MM), and in most cases, is assumed to be caused by direct invasion of myeloma cells into the peritoneal cavity, as suggested by exudative effusion and a high proportion of myeloma cells (1-3). This is in contrast to pleural effusion, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes (POEMS) syndrome, another type of plasma cell dyscrasia, in which ascites is more common and which may be caused by the aberrant secretion of vascular endothelial growth factor (VEGF). Although VEGF is also secreted by MM cells, its relationship with the symptoms of MM is poorly elucidated. In the present case, the serum and ascitic levels of VEGF were significantly elevated and decreased after chemotherapy for MM. The decrease in the levels occurred alongside a reduction in the amount ascites, suggesting that the elevation VEGF may be associated with the formation of ascites.

Case Report

A 43-year-old man presented to our hospital for anemia in 2009 and was diagnosed with MM [immunoglobulin (Ig) G kappa type, Durie Salmon stage I]. Although a bone marrow examination showed 6% plasma cells, we diagnosed the patient with symptomatic myeloma due to the presence of monoclonal gammopathy and associated symptoms (i.e., anemia). Pathological immunostaining showed kappa-deviated restriction. A surface marker analysis showed that the myeloma cells were positive for CD56 and IgG and negative for CD20, CD79a, IgA, IgM, and cycline-D1. A chromosomal examination revealed a normal karyotype. A few months after the diagnosis, the patient developed massive ascites. Abdominal paracentesis revealed clear, non-bloody fluids. A laboratory analysis of the ascites fluid revealed the following: white blood cell (WBC) count, 500/mL; total protein (TP), 6.5 g/dL; lactate dehydrogenase (LDH), 66 IU/L; and glucose, 95 mg/dL, which corresponded to transudates. Wright's staining of a centrifuged

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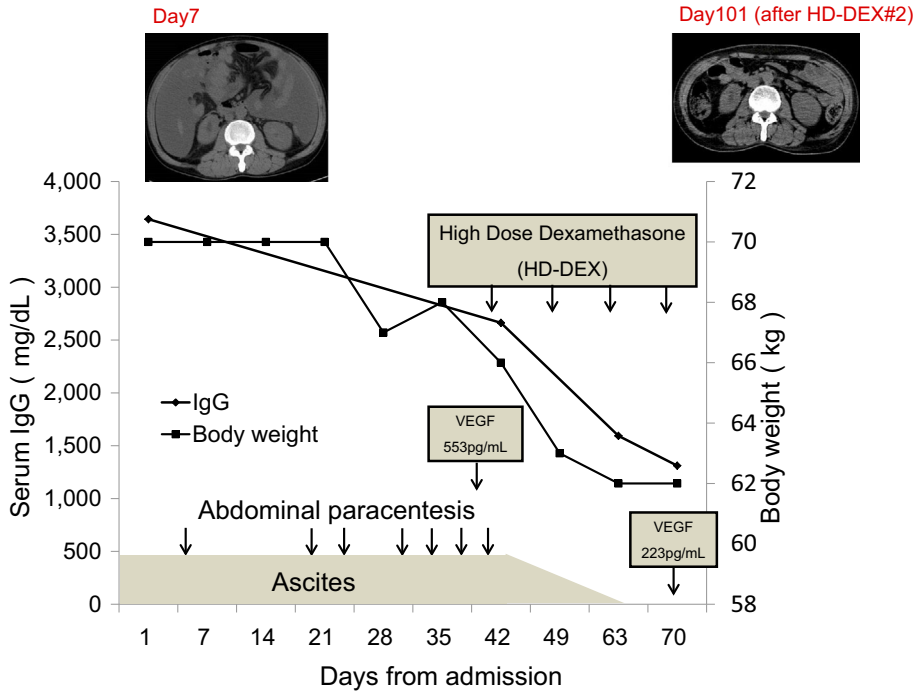

Figure. **The clinical course of the present case. The volume of ascites significantly increased, causing the need for regular abdominal paracentesis (once or twice a week) to palliate abdominal distension. After high-dose dexamethasone therapy, the ascites volume decreased; this was accompanied by reductions in the patient's serum IgG and VEGF levels. VEGF: vascular endothelial growth factor**

Table. **Previous Reports of VEGF Levels in MM and POEMS Syndrome Patients.**

Reference	Patients number	Serum VEGF levels (normal range <38.3, pg/mL mean±SD)
10 (POEMS)	21	403±245
11 (MM)	57	273.5±179.1
12 (MM)	14	239

VEGF: vascular endothelial growth factor, MM: multiple myeloma, POEMS: pleural effusion, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, skin changes, SD: standard deviation

ascites sample revealed that the cells were mainly composed of neutrophils and only 2% plasma cells. Bacterial cultures were all negative, and empiric antibiotic therapy did not reduce the volume of ascites. No organ dysfunction that could account for transudative ascites was detected (including hepatic, renal, or cardiac failure). The IgG level, blood counts, and bone marrow findings did not suggest the progression of MM. Thus, we focused on VEGF as a causative agent, as it is related to ascites in POEMS syndrome (4).

There were no characteristic symptoms (i.e., polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, or skin changes) in our case, with the exception of monoclonal gammopathy. We therefore hypothesized that that patients with MM may develop pathophysiological conditions that are similar to those associated with VEGF.

Both the serum and ascites showed increased VEGF levels [553 pg/mL in serum (normal range <38.3 pg/mL); 988.0 pg/mL in ascites (normal range not set)]. We considered the elevated VEGF level and ascites to be signs of the progression of myeloma, and decided to start chemotherapy. After the administration of high-dose dexamethasone therapy (40 mg/body/day on days 1-4, 9-12, and 17-20), there was a marked decrease in the volume of ascites, the serum VEGF levels decreased to 223 pg/mL, and the patient's MM showed a partial response (the IgG level decreased from 3,644 mg/dL to 1,593 mg/dL) (Figure). Bone marrow aspiration (BMA) showed almost normocellular bone marrow with a marked decrease in the proportion of plasma cells (proportion of myeloma cells reduced to <1%). After discharge, the patient's IgG levels declined continuously during 4 courses of high-dose dexamethasone therapy; this was accompanied by a recovery of the patient's Hb and albumin levels (Hb: from 8.0 g/dL to 14.0 g/dL; albumin: from 2.5 g/dL to 3.5 g/dL). At 6 months after discharge (with follow-up), the patient was transferred to another hospital for autologous peripheral blood stem cell transplantation (auto-PBSCT).

Discussion

VEGF induces vessel hyperpermeability and leads to the retention of pleural effusion. In certain solid tumors, reports suggest an association between malignant ascites and elevated VEGF levels (5). Elevated ascitic VEGF levels are useful to distinguish between malignant and nonmalignant ascites, such as ascites associated with liver cirrhosis (6). Although the secretion and production of VEGF have been documented in myeloma cells (7, 8) (Table), the elevation is

generally modest and rarely reaches the level seen in the current case (9). Given the very high levels of VEGF that were observed in this case as well as in POEMS syndrome (10), the development of ascites may be associated with the high VEGF levels. The marked reduction of ascites in our case correlated well with the decrease in the serum VEGF level, and supports that VEGF plays a role in the development of ascites, similar to its role in POEMS syndrome.

In solid tumors, malignant pleural effusion is known to result from the elevation of the serum level of VEGF, and the inhibition of VEGF by its antibody, bevacizumab, which prevents the accumulation of VEGF (11, 12).

In MM, limited reports suggest that the combination of bevacizumab with conventional chemotherapy seems to have little effect in suppressing the progression of the disease (13). However, some reports have shown the efficacy of bevacizumab as an adjunctive treatment to regional plasmacytoma expressing aberrant VEGF (14, 15). Taken together with these reports and our case, the pleural effusion that develops in association with a high level of VEGF in patients with MM might respond to the administration of combination treatment that includes bevacizumab. Further investigations, including the verification of the correlation between the serum VEGF levels and the development of ascites in MM, is needed to confirm this causal relationship.

In conclusion, our case suggests that elevated VEGF levels may be responsible for the manifestation of ascites in MM.

The authors state that they have no Conflict of Interest (COI).

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